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(54) **CHROMATOGRAPHY SYSTEM WITH WASTE OUTPUT**

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(73) Assignee: **Agilent Technologies, Inc.**

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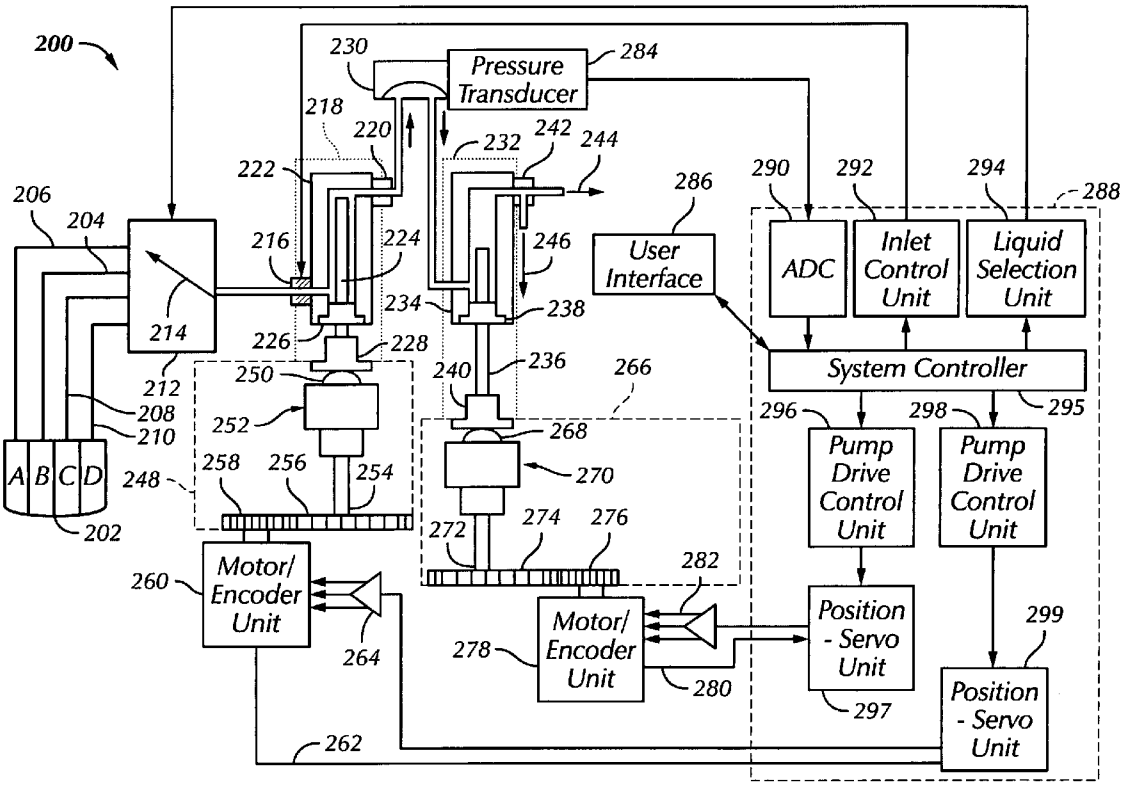
F04B 49/00 (2006.01)

(52) **U.S. Cl.** **73/61.56**; 700/282; 417/216

(57) **ABSTRACT**

A variety of methods for operating a chromatography system are presented. Specifically, methods for operating a pumping system within a chromatography system are presented. The methods presented are directed to pumping apparatus in which very small amounts of fluid are pumped through the system. A number of techniques for detecting and compensating for leaks are presented as well as a number of techniques for operating the pumping system.



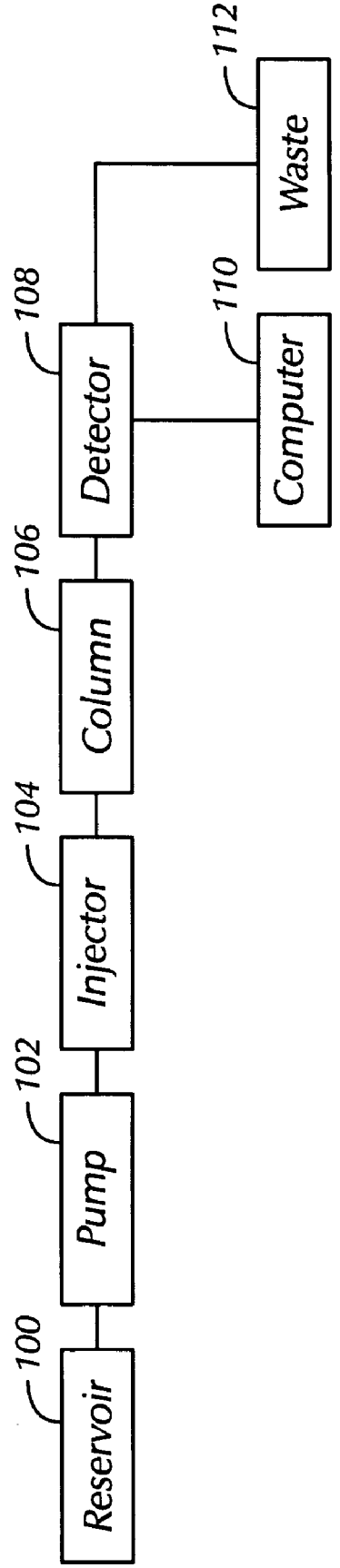
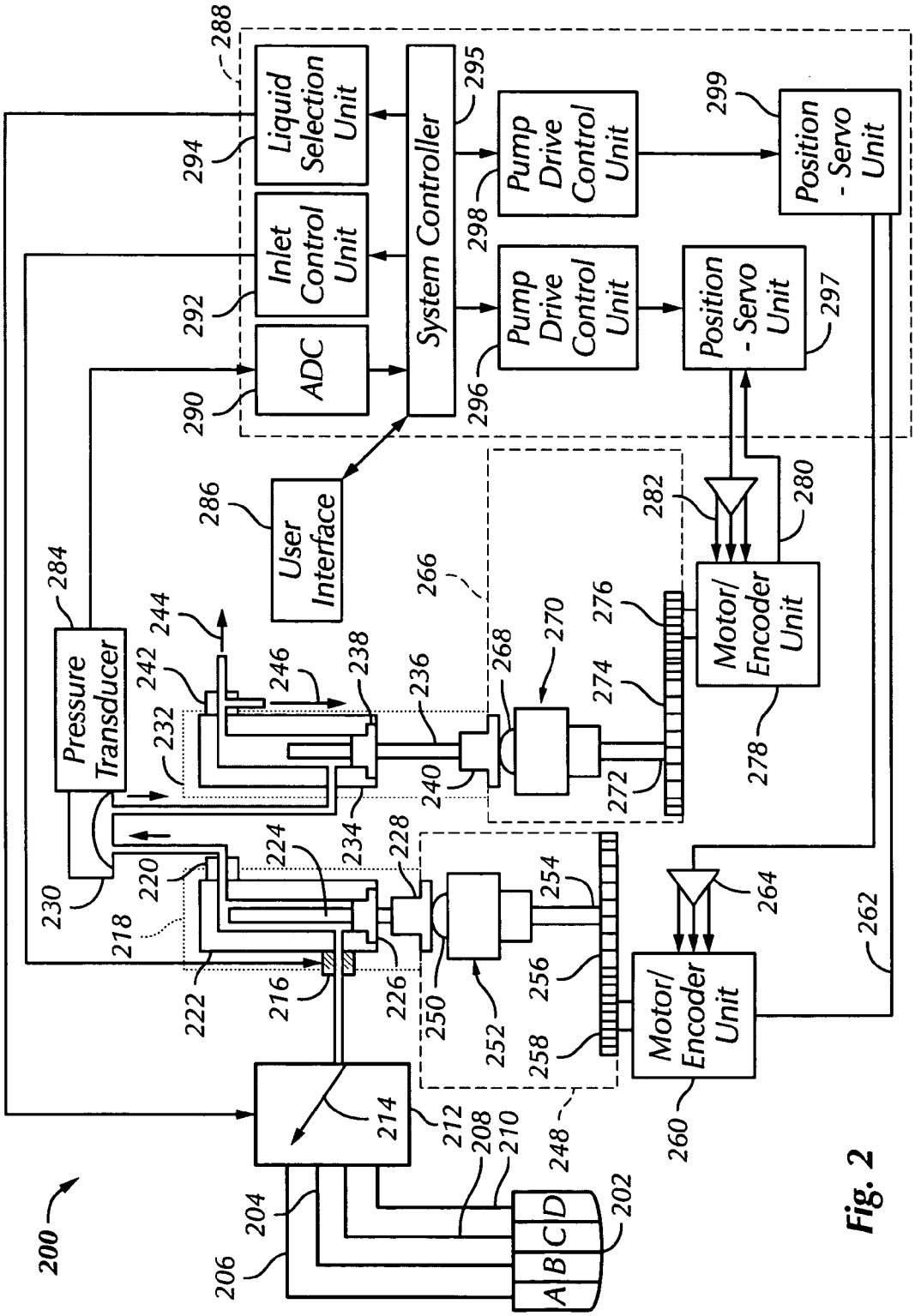


Fig. 1
(Prior Art)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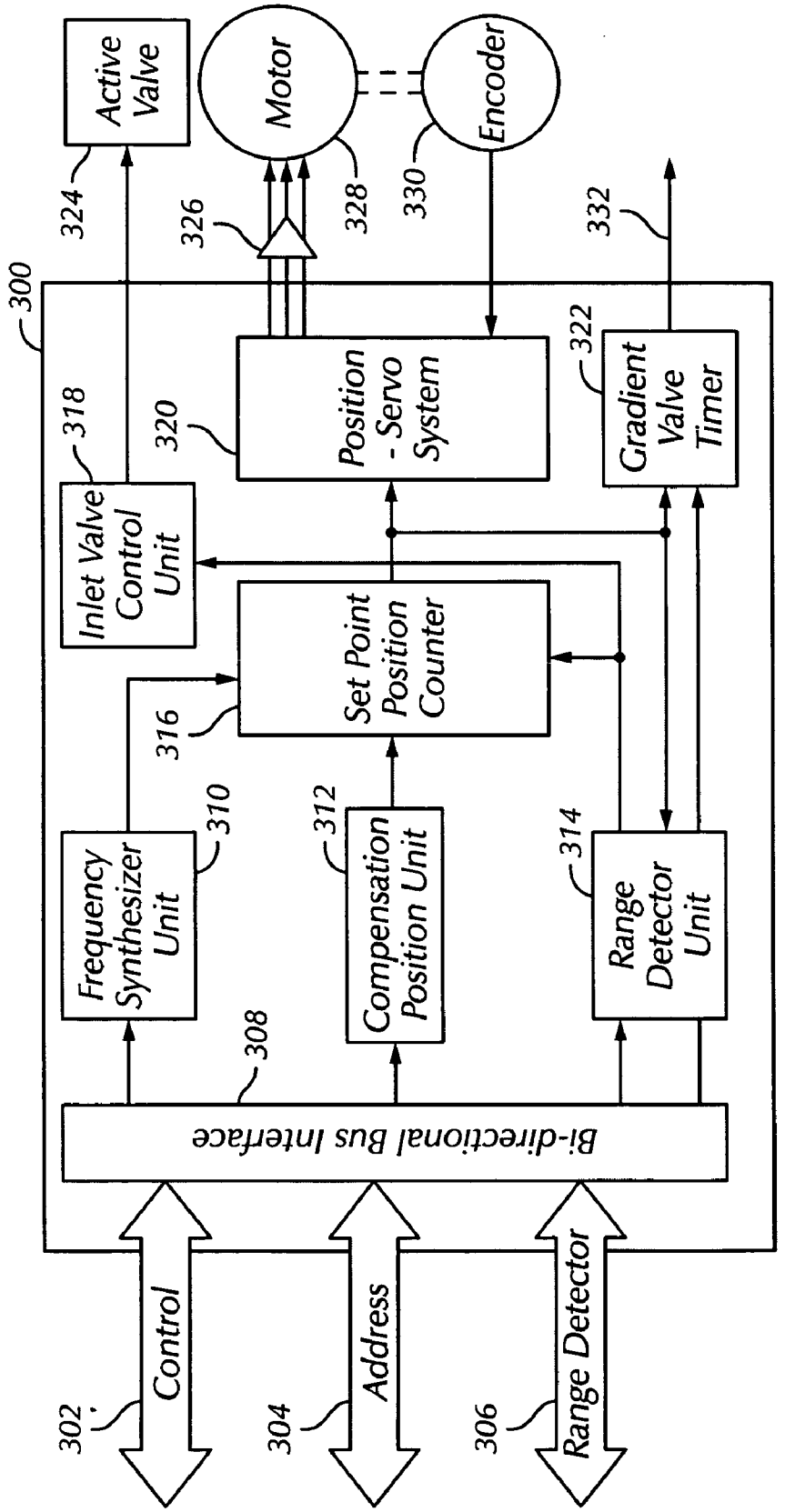
276
278
280
282
284
286
288
290
292
294
295
296
297
298
299
A
B
C
D
ADC
Inlet Control Unit
Liquid Selection Unit
System Controller
Pump Drive Control Unit
Pump Drive Control Unit
Position - Servo Unit
Position - Servo Unit
User Interface
Pressure Transducer
Motor/ Encoder Unit
Motor/ Encoder Unit

Fig. 2


Active Valve
Motor
Encoder
324
326
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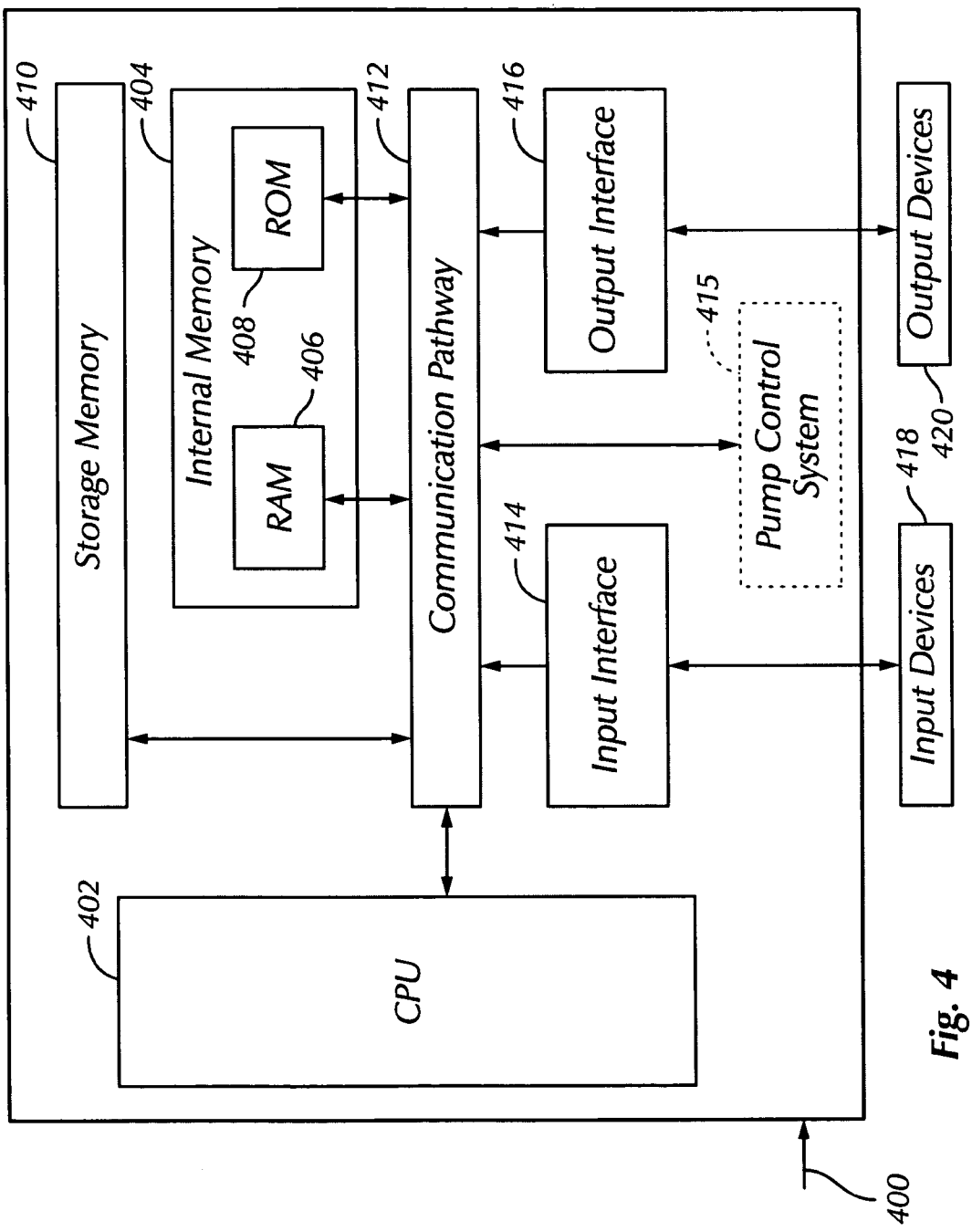
300
318
320
322
Position - Servo System
Gradient Valve Timer
Inlet Valve Control Unit
Set Point Position Counter
316
310
312
314
Frequency Synthesizer Unit
Compensation Position Unit
Range Detector Unit
308
Bi-directional Bus Interface
302
304
306
Control
Address
Range Detector

Fig. 3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CPU
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Storage Memory
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Internal Memory
404
ROM
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RAM
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Communication Pathway
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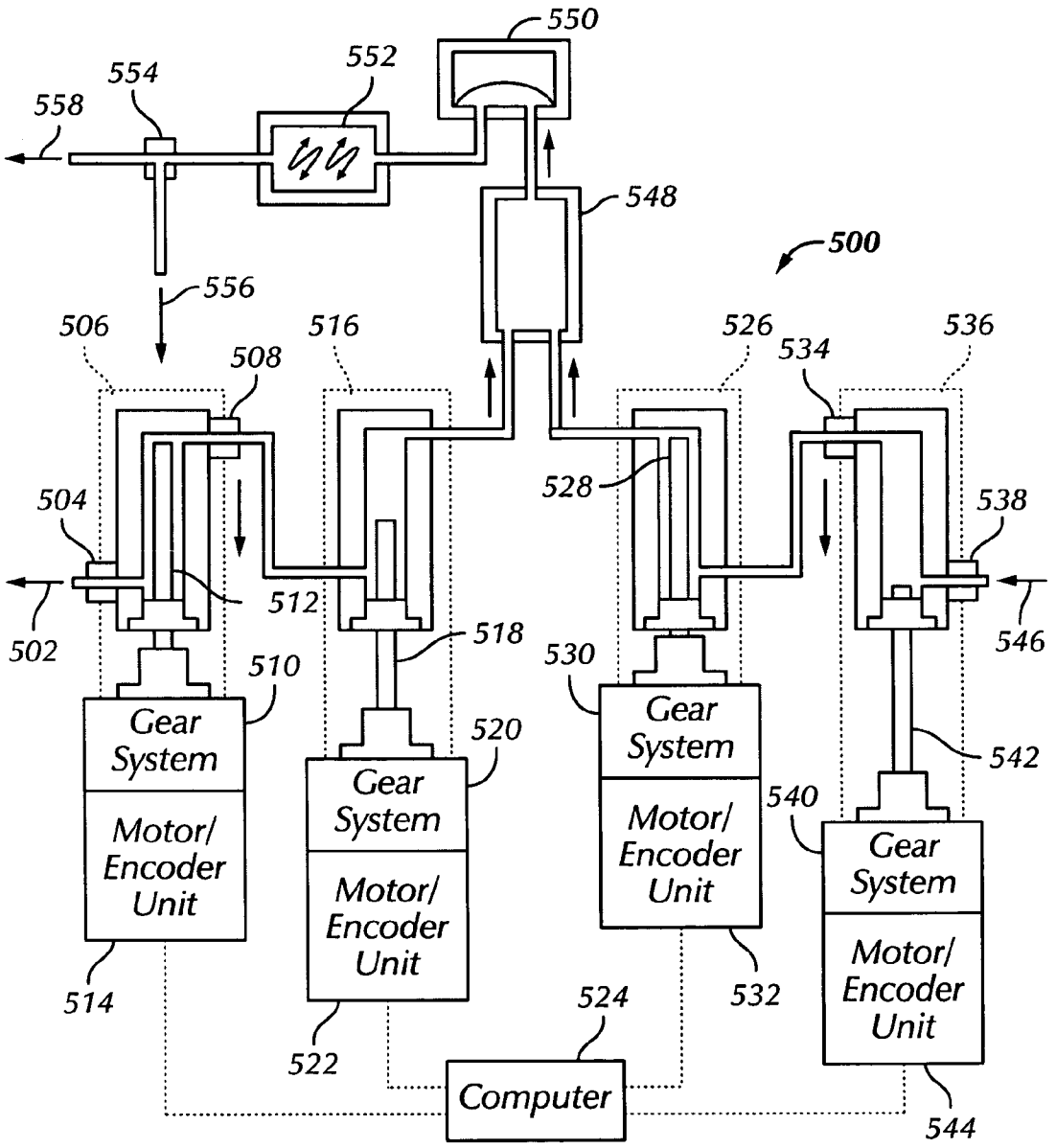
Input Interface
414
Output Interface
416
Pump Control System
415
Input Devices
418
Output Devices
420

Fig. 4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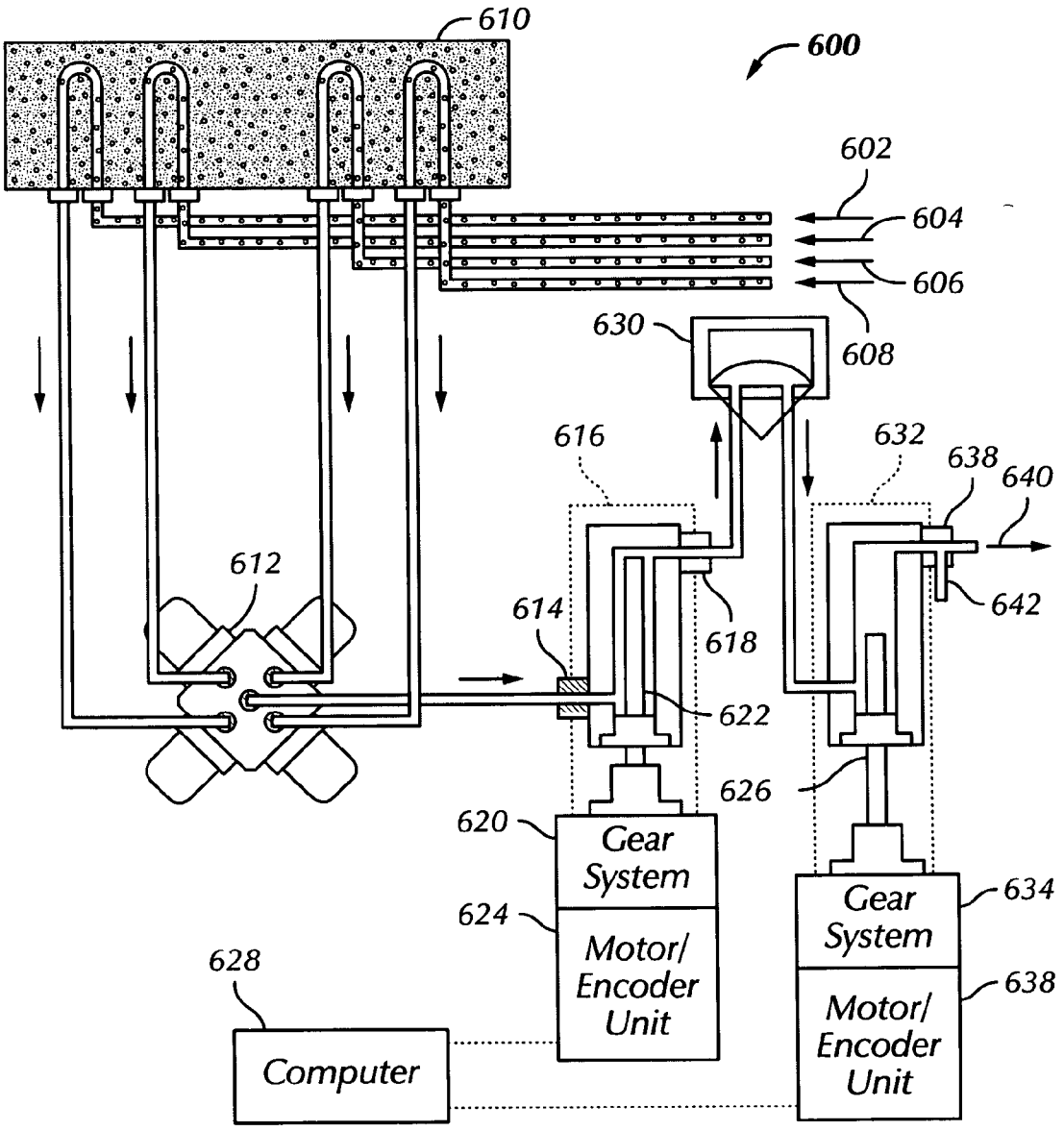
530
Gear System
Motor/ Encoder Unit
520
542
540
514
532
524
522
Computer
544

Fig. 5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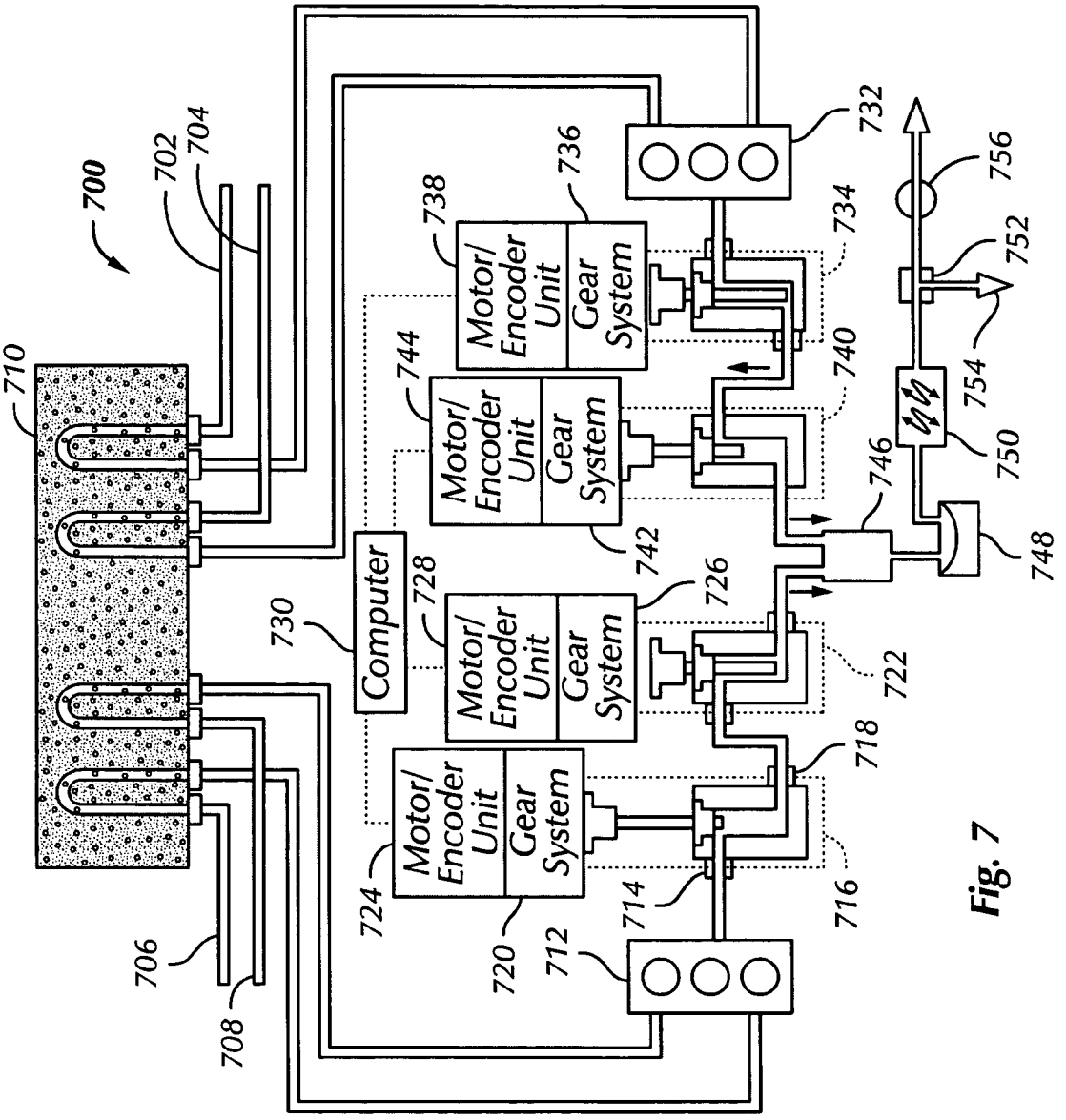
620
Gear System
624
Motor/ Encoder Unit
634
628
Computer
638
Gear System
Motor/ Encoder Unit

Fig. 6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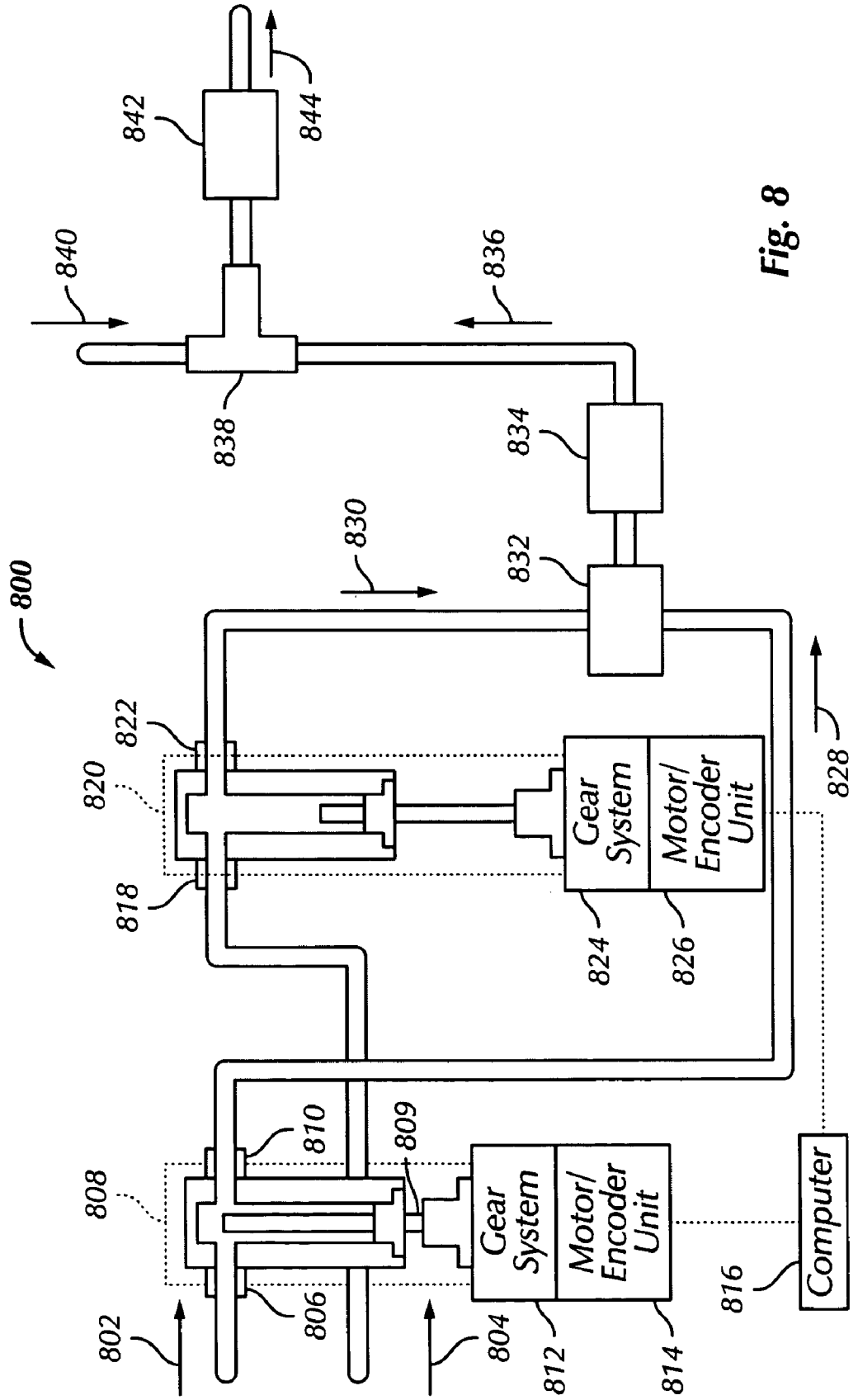
748
750
752
754
756
Computer
Motor/ Encoder Unit
Gear System

Fig. 7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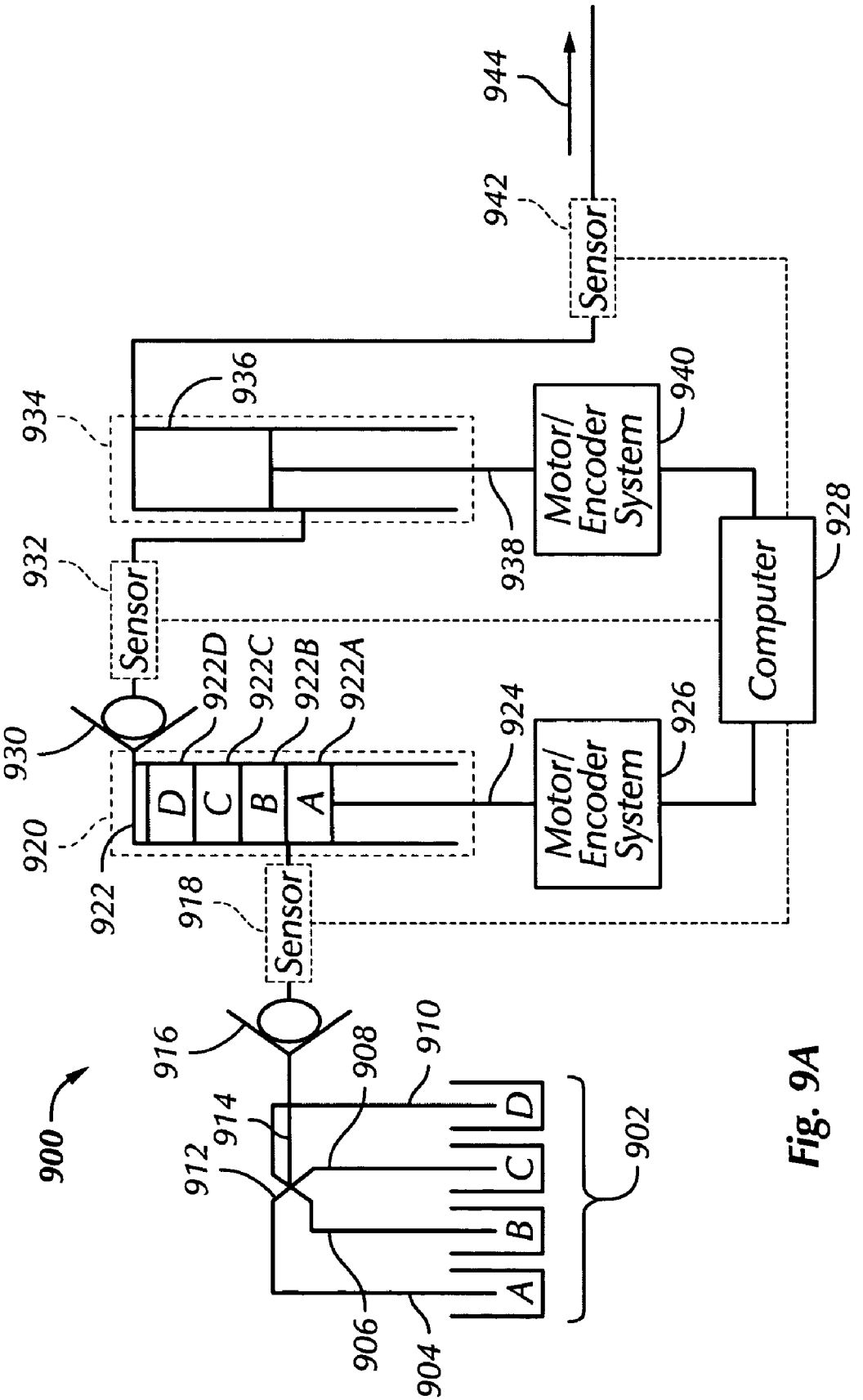
838
840
842
844
Gear System
Motor/ Encoder Unit
Gear System
Motor/ Encoder Unit
Computer

Fig. 8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922A
922B
922C
922D
924
926
928
930
932
934
936
938
940
942
944
A
B
C
D
Sensor
Sensor
Sensor
Motor/ Encoder System
Motor/ Encoder System
Computer

Fig. 9A

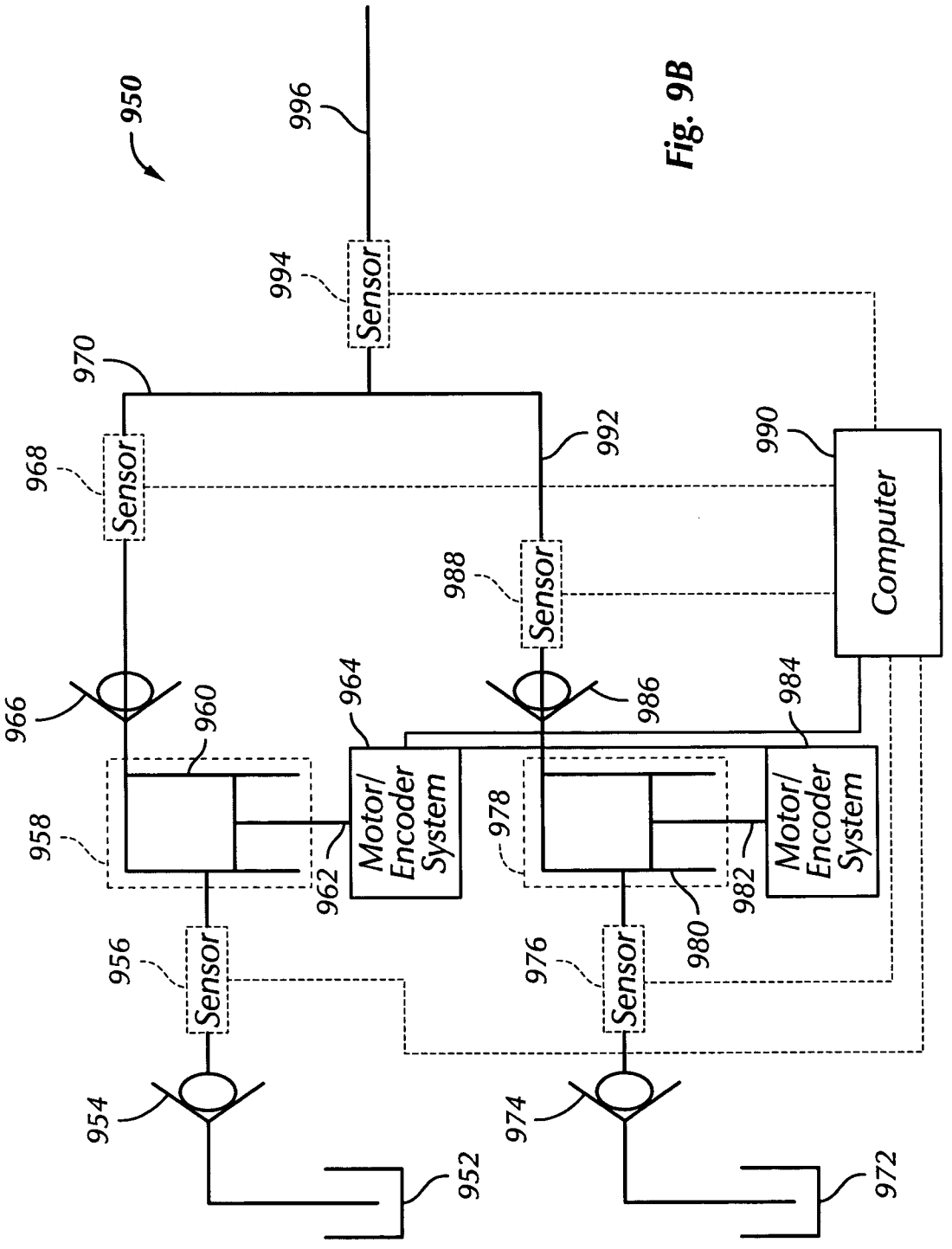
950
996
994
Sensor
970
968
Sensor
992
990
Computer
988
Sensor
966
960
964
986
984
958
962
Motor/
Encoder
System
978
982
Motor/
Encoder
System
956
Sensor
980
976
Sensor
954
974
952
972

Fig. 9B

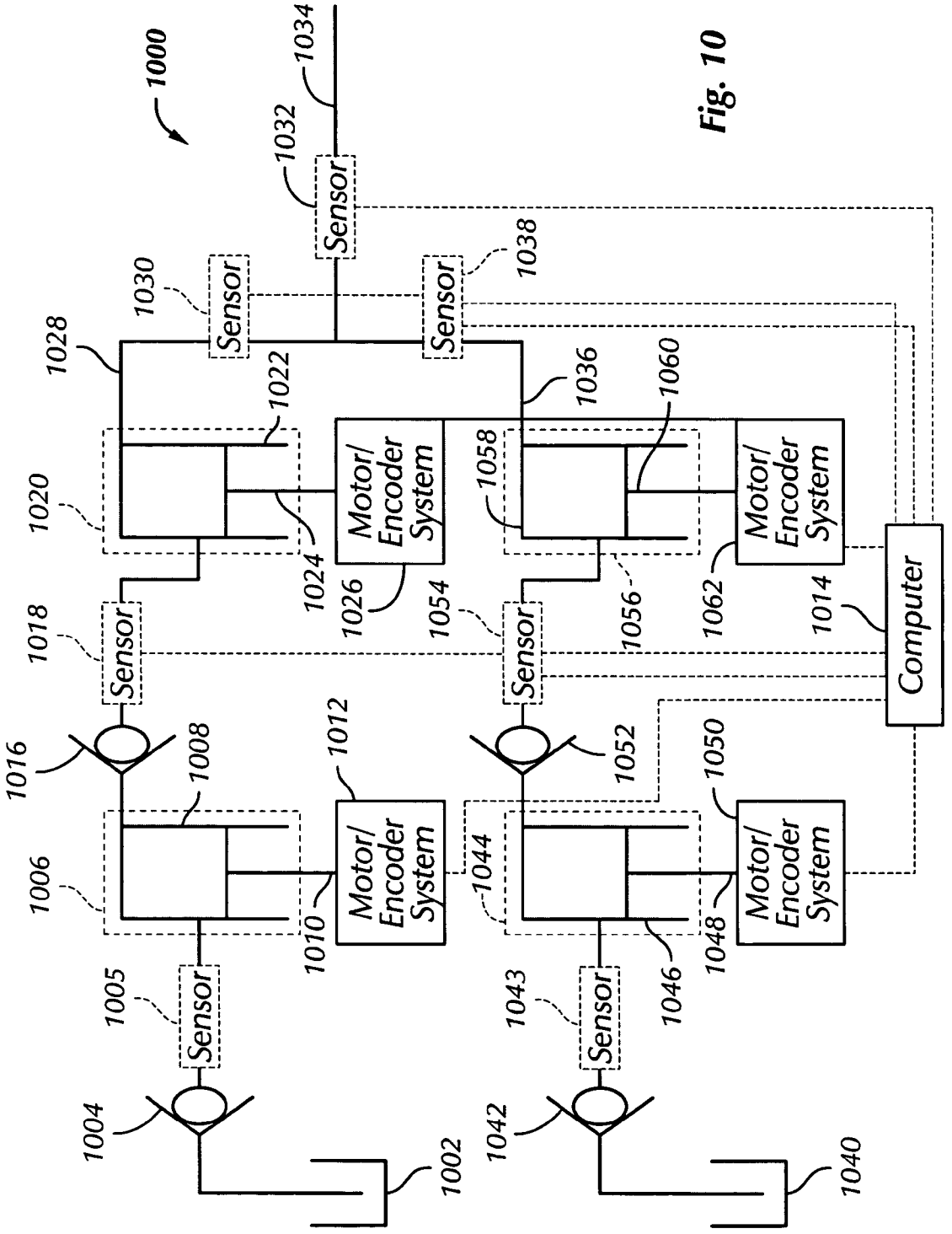
1000
1034
1032
Sensor
1030
Sensor
1038
Sensor
1028
1022
1036
1060
1020
Motor/ Encoder System
1058
Motor/ Encoder System
1024
1026
1054
1056
1062
1014
Computer
1018
Sensor
Sensor
1016
1008
1012
1052
1050
1006
Motor/ Encoder System
1044
Motor/ Encoder System
1010
1048
1005
Sensor
1043
Sensor
1046
1004
1042
1002
1040

Fig. 10

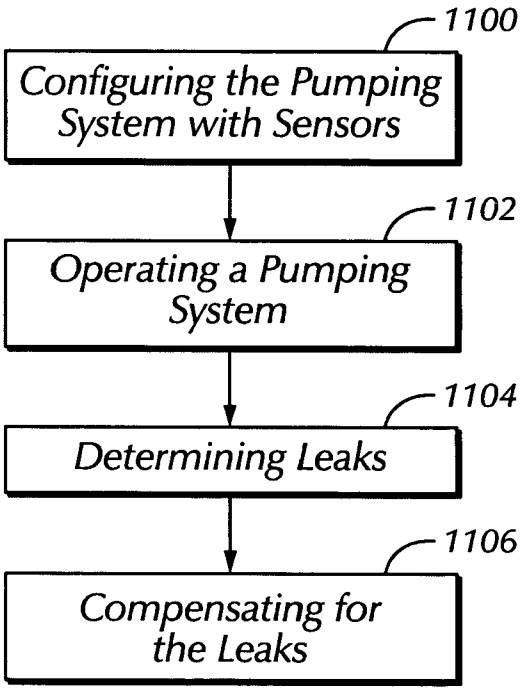

Fig. 11A

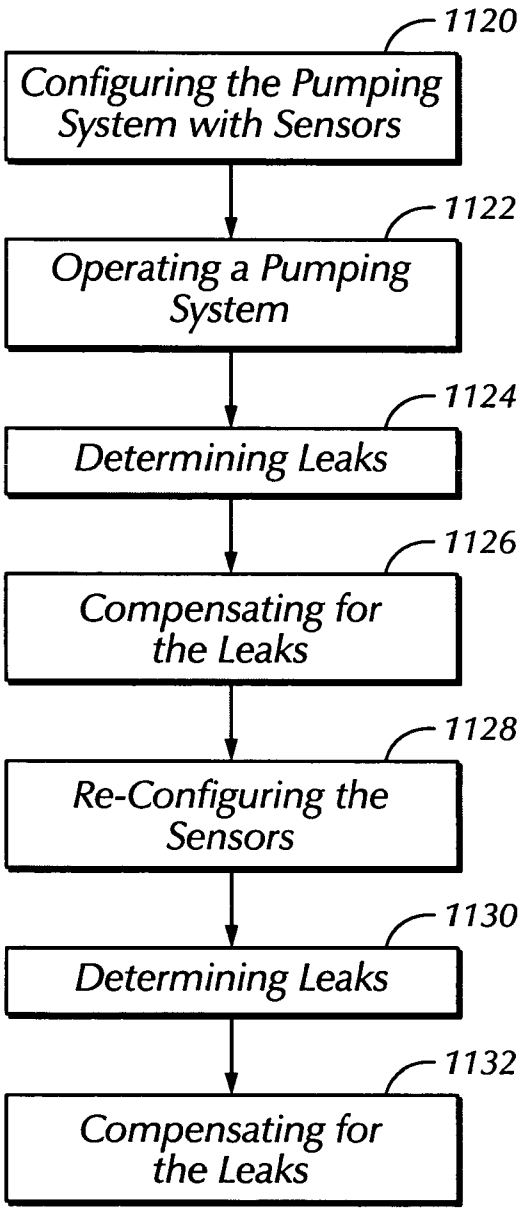

Fig. 11B

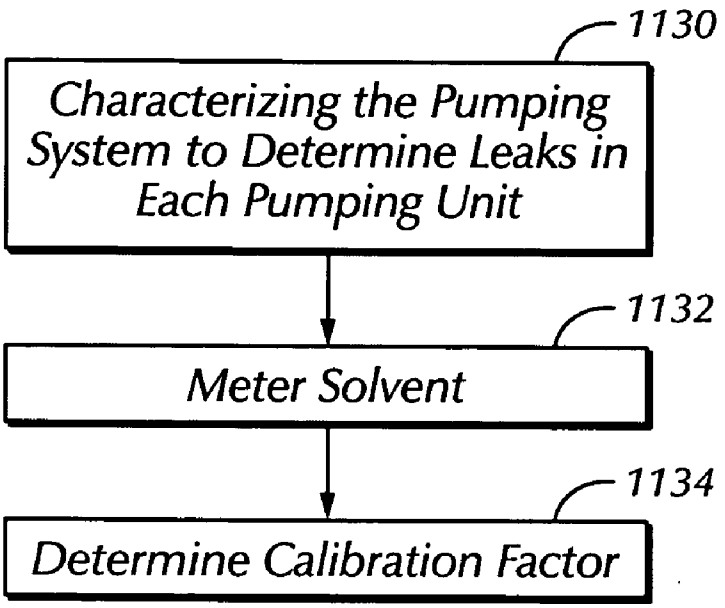

Fig. 11C

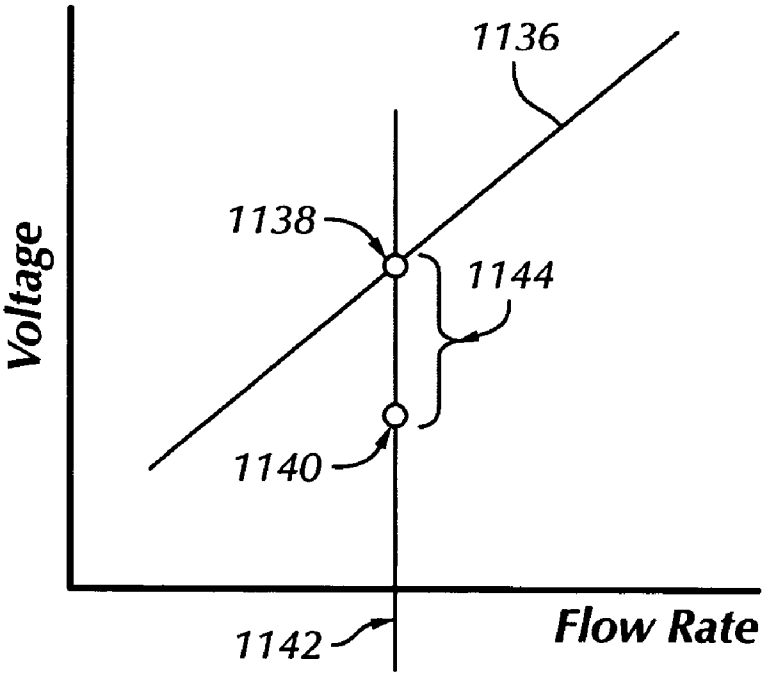

Fig. 11D

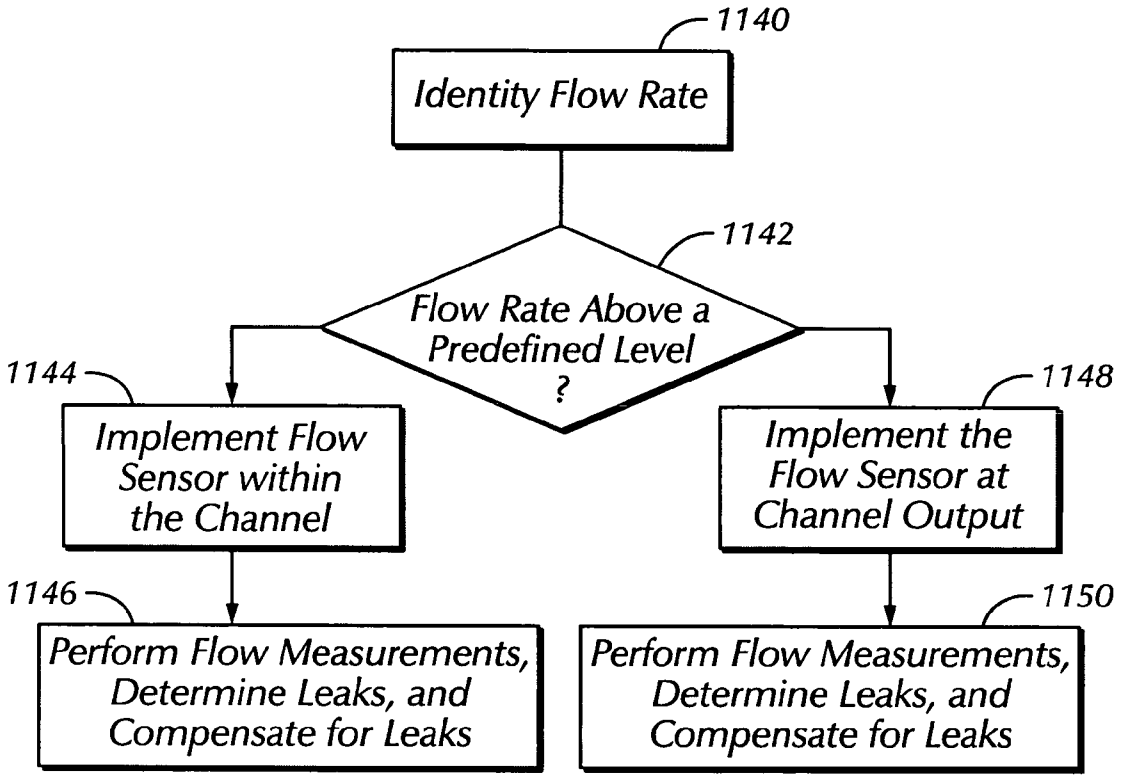
1140
Identity Flow Rate
1142
Flow Rate Above a Predefined Level ?
1144
Implement Flow Sensor within the Channel
1146
Perform Flow Measurements, Determine Leaks, and Compensate for Leaks
1148
Implement the Flow Sensor at Channel Output
1150
Perform Flow Measurements, Determine Leaks, and Compensate for Leaks

Fig. 11E

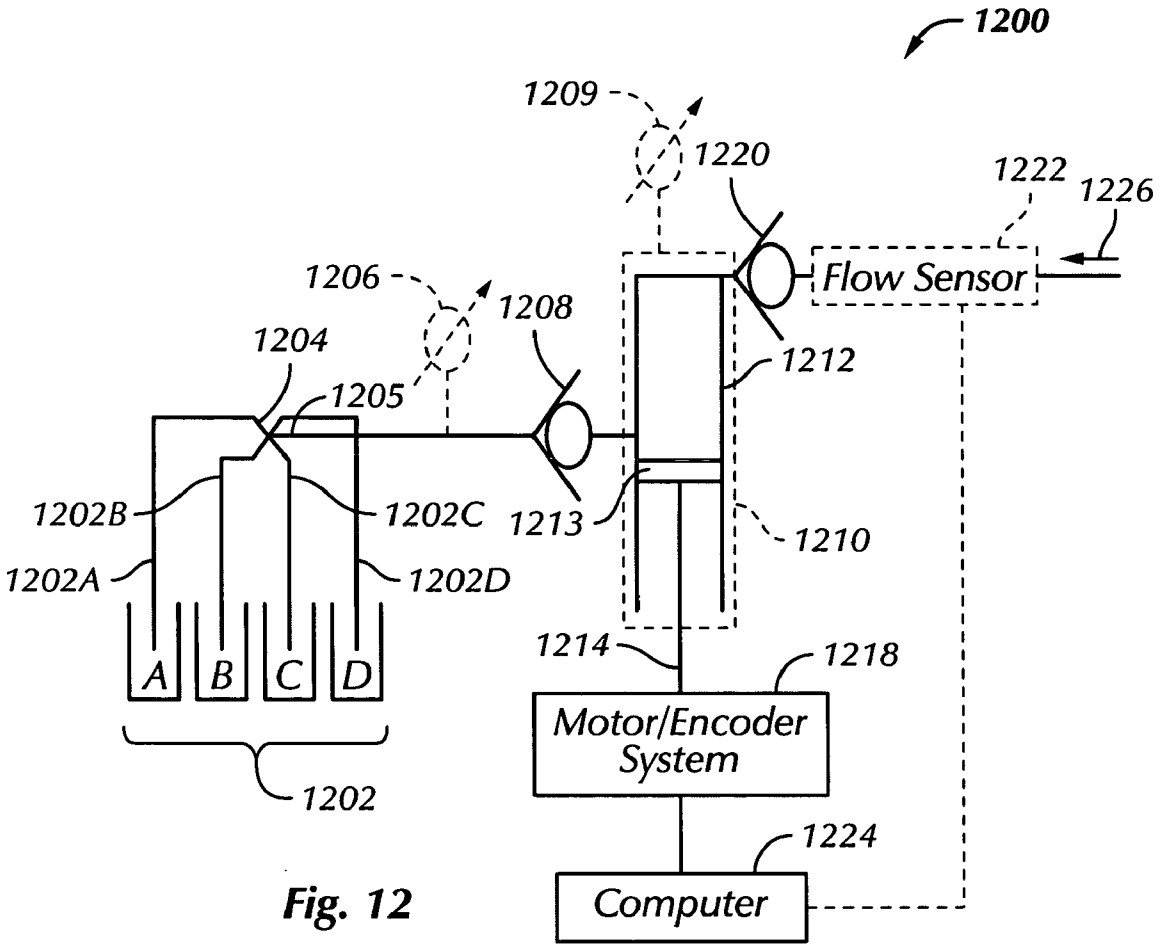
1200
1209
1220
1222
1226
Flow Sensor
1206
1208
1204
1205
1212
1202B
1202C
1213
1210
1202A
1202D
A
B
C
D
1214
1218
Motor/Encoder System
1202
1224
Computer

Fig. 12

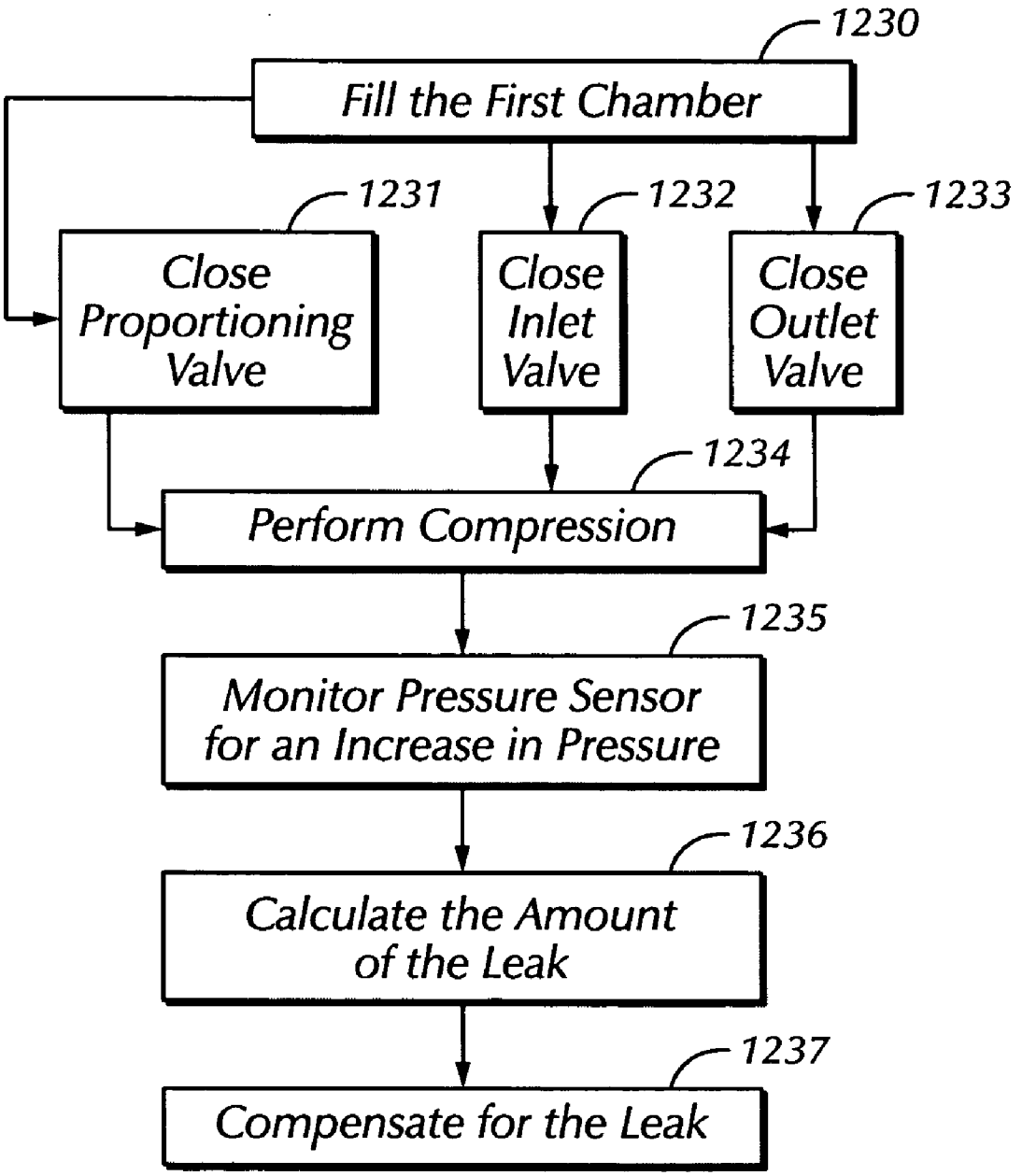
1230
Fill the First Chamber
1231
1232
1233
Close Proportioning Valve
Close Inlet Valve
Close Outlet Valve
1234
Perform Compression
1235
Monitor Pressure Sensor for an Increase in Pressure
1236
Calculate the Amount of the Leak
1237
Compensate for the Leak

Fig. 12A

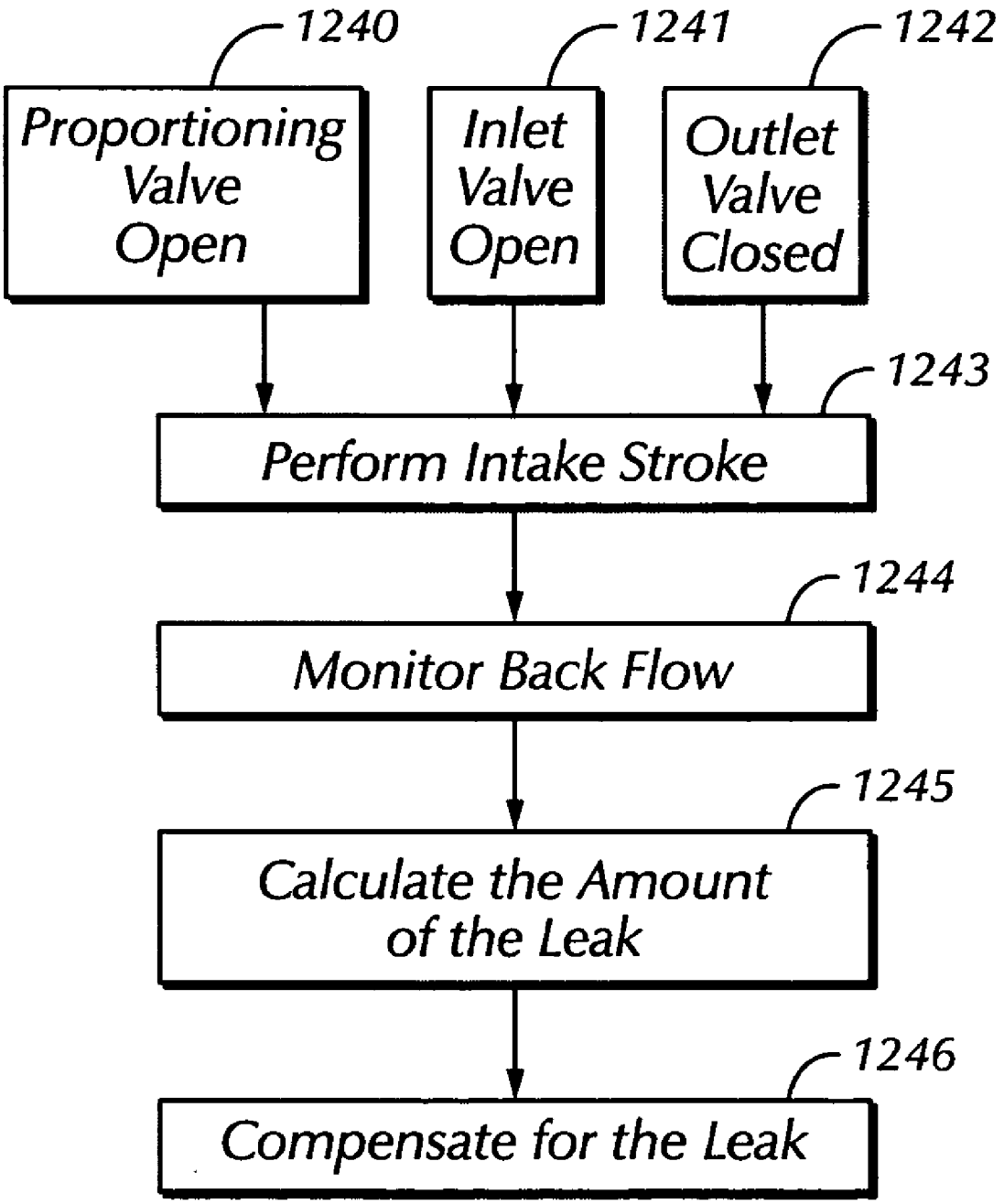
1240
1241
1242
Proportioning Valve Open
Inlet Valve Open
Outlet Valve Closed
1243
Perform Intake Stroke
1244
Monitor Back Flow
1245
Calculate the Amount of the Leak
1246
Compensate for the Leak

Fig. 12B

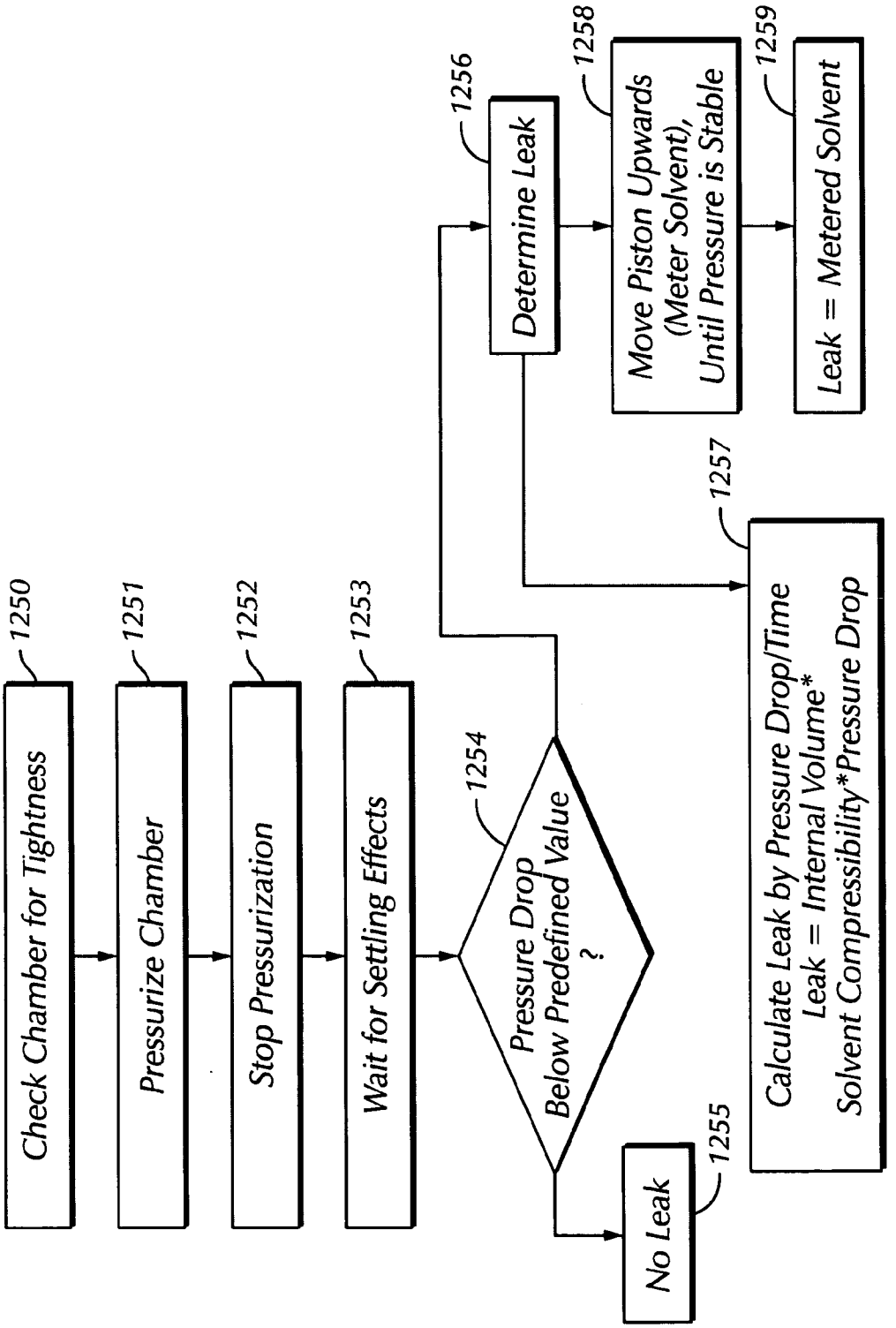
1250
Check Chamber for Tightness
1251
Pressurize Chamber
1252
Stop Pressurization
1253
Wait for Settling Effects
1254
Pressure Drop Below Predefined Value ?
1255
No Leak
1256
Determine Leak
1257
Calculate Leak by Pressure Drop/Time
Leak = Internal Volume*
Solvent Compressibility*Pressure Drop
1258
Move Piston Upwards (Meter Solvent), Until Pressure is Stable
1259
Leak = Metered Solvent

Fig. 12C

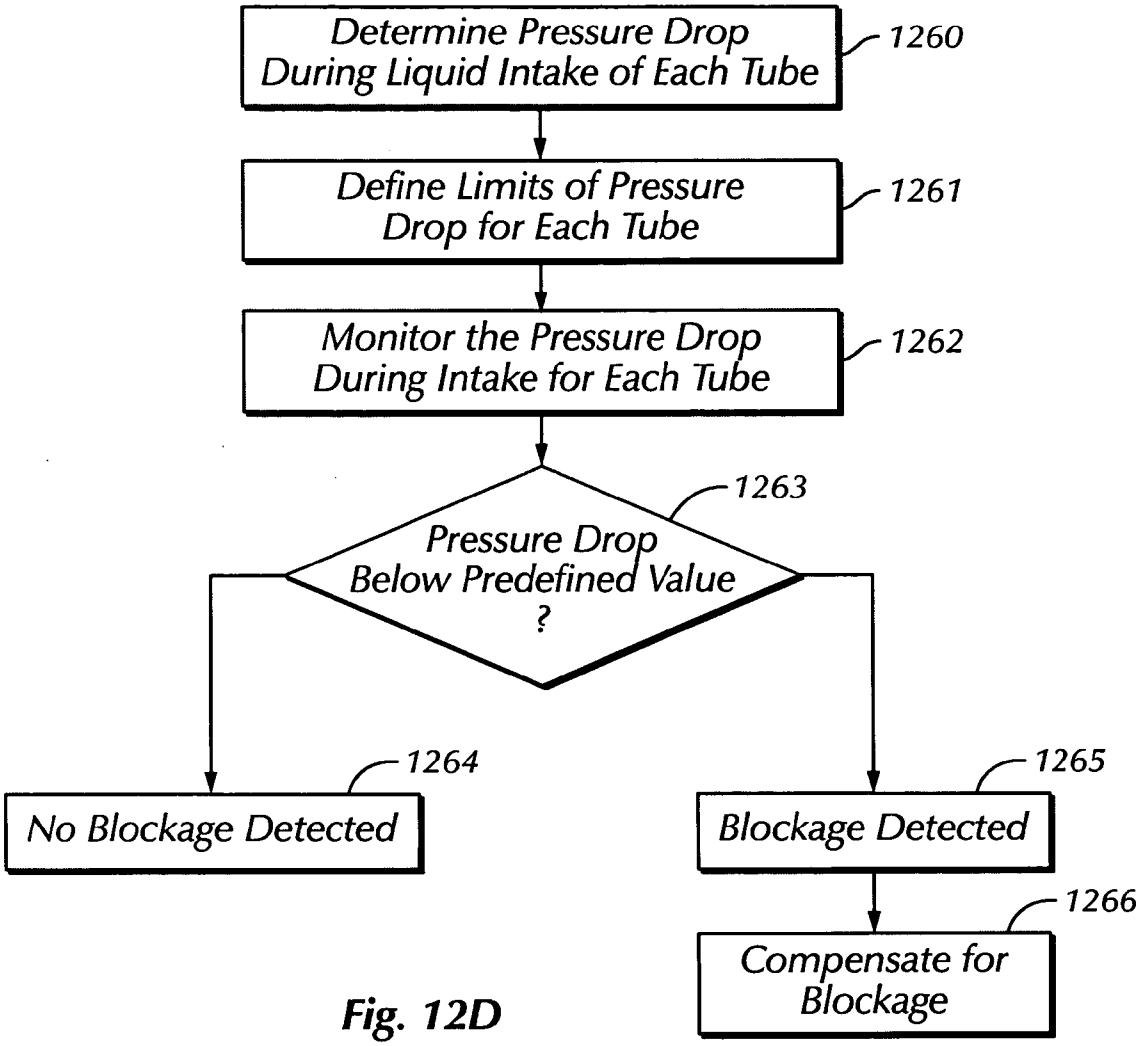
Determine Pressure Drop During Liquid Intake of Each Tube
1260
Define Limits of Pressure Drop for Each Tube
1261
Monitor the Pressure Drop During Intake for Each Tube
1262
Pressure Drop Below Predefined Value ?
1263
No Blockage Detected
1264
Blockage Detected
1265
Compensate for Blockage
1266

Fig. 12D

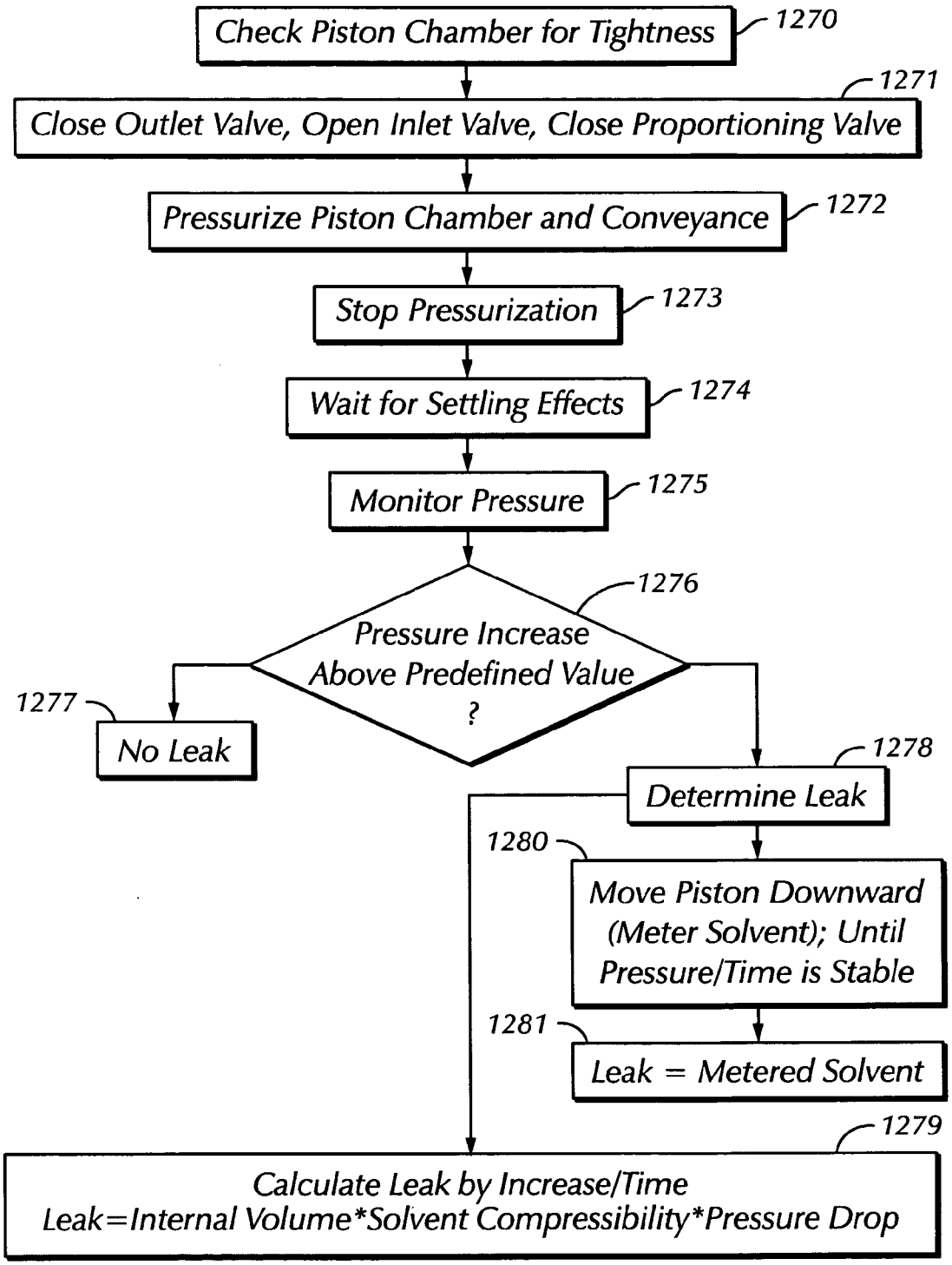
Check Piston Chamber for Tightness
1270
Close Outlet Valve, Open Inlet Valve, Close Proportioning Valve
1271
Pressurize Piston Chamber and Conveyance
1272
Stop Pressurization
1273
Wait for Settling Effects
1274
Monitor Pressure
1275
Pressure Increase Above Predefined Value ?
1276
1277
No Leak
1278
Determine Leak
1280
Move Piston Downward (Meter Solvent); Until Pressure/Time is Stable
1281
Leak = Metered Solvent
1279
Calculate Leak by Increase/Time
Leak=Internal Volume*Solvent Compressibility*Pressure Drop

Fig. 12E

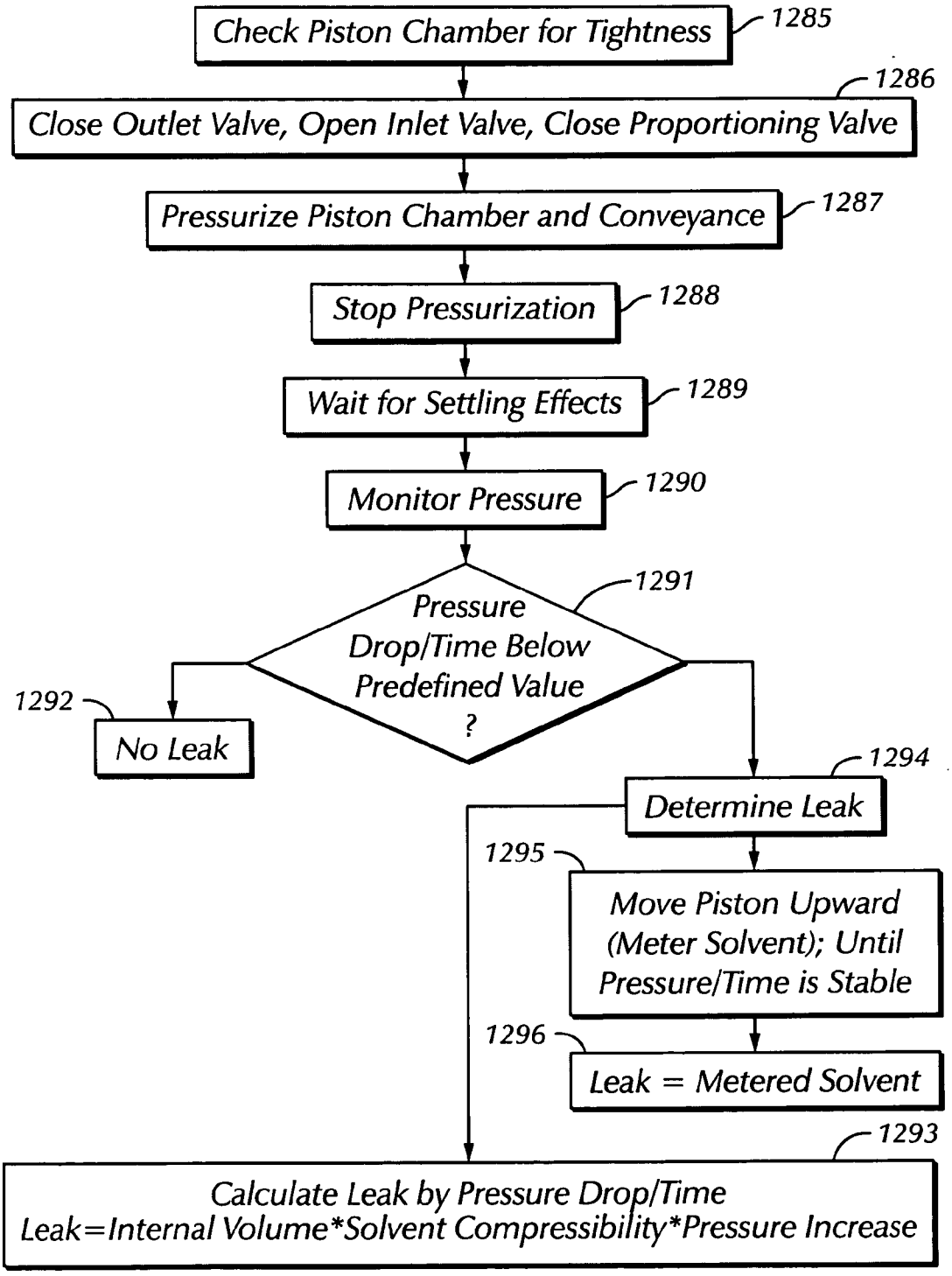
Check Piston Chamber for Tightness
1285
Close Outlet Valve, Open Inlet Valve, Close Proportioning Valve
1286
Pressurize Piston Chamber and Conveyance
1287
Stop Pressurization
1288
Wait for Settling Effects
1289
Monitor Pressure
1290
Pressure Drop/Time Below Predefined Value ?
1291
1292
No Leak
1294
Determine Leak
1295
Move Piston Upward (Meter Solvent); Until Pressure/Time is Stable
1296
Leak = Metered Solvent
1293
Calculate Leak by Pressure Drop/Time
Leak=Internal Volume*Solvent Compressibility*Pressure Increase

Fig. 12F

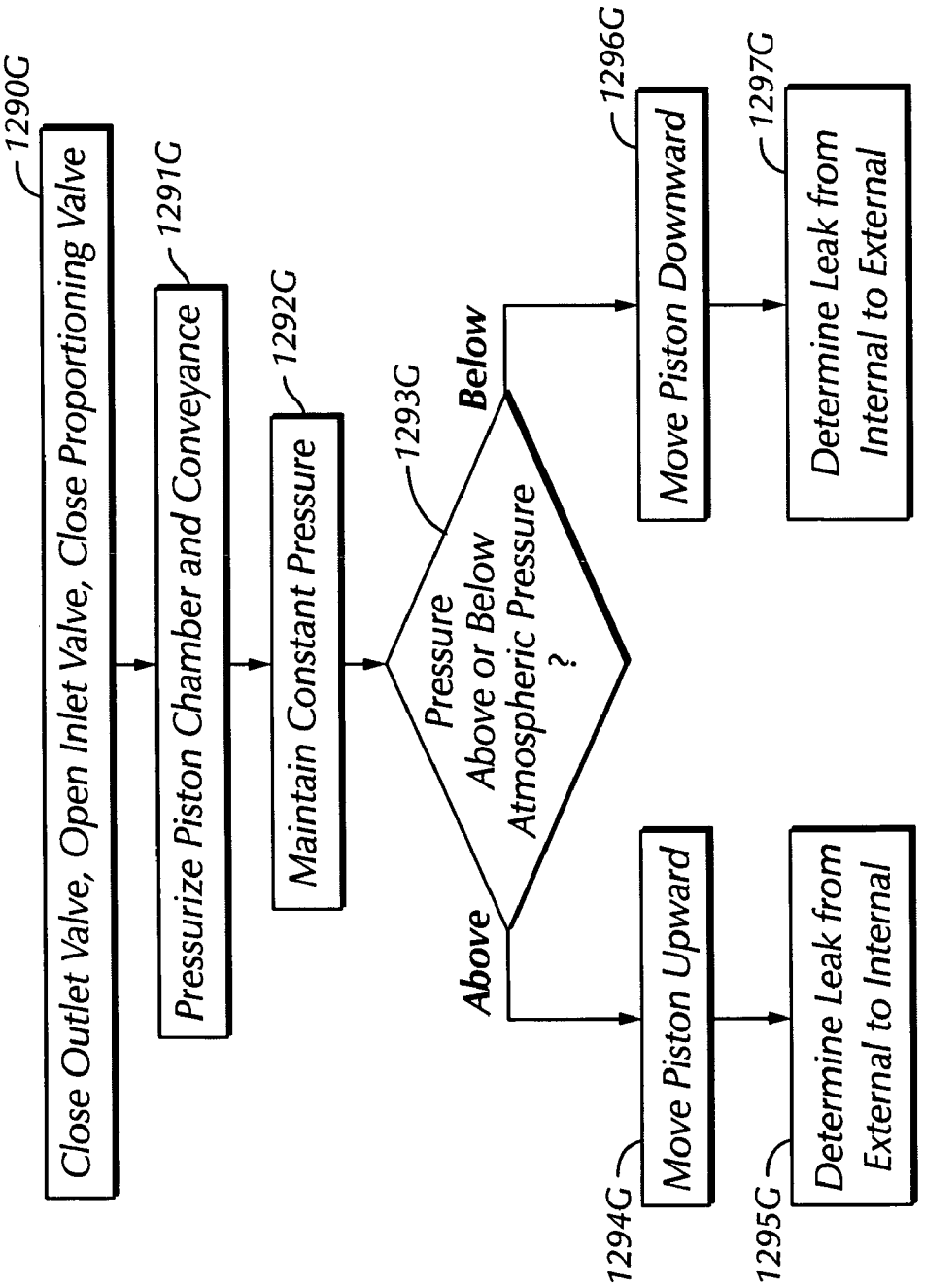
1290G
Close Outlet Valve, Open Inlet Valve, Close Proportioning Valve
1291G
Pressurize Piston Chamber and Conveyance
1292G
Maintain Constant Pressure
1293G
Pressure Above or Below Atmospheric Pressure ?
Above
Below
1294G
Move Piston Upward
1295G
Determine Leak from External to Internal
1296G
Move Piston Downward
1297G
Determine Leak from Internal to External

Fig. 12G

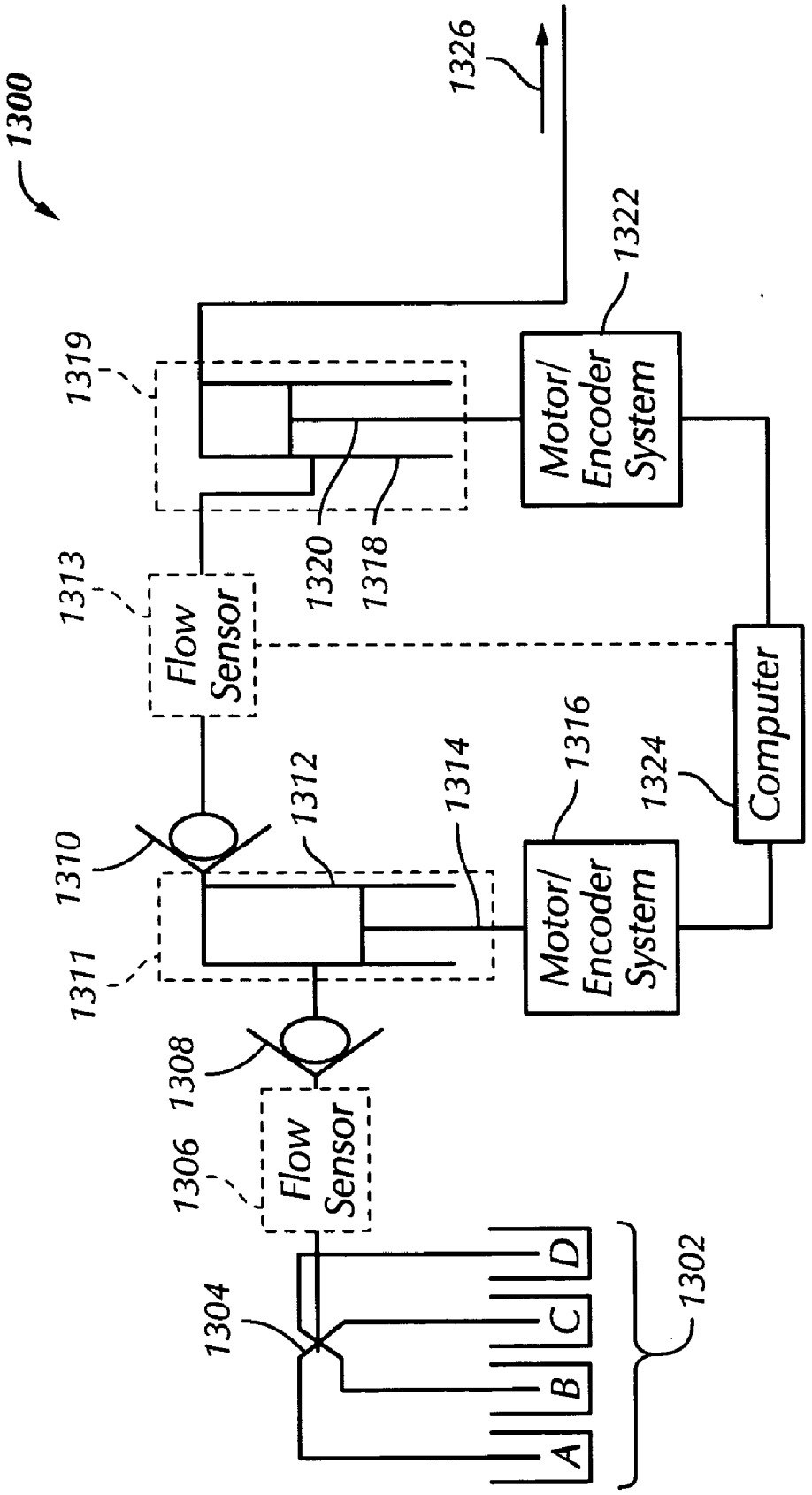
1300
1326
1322
Motor/ Encoder System
1319
1320
1318
1313
Flow Sensor
Computer
1316
1324
1312
1314
1310
1311
Motor/ Encoder System
1308
1306
Flow Sensor
1304
A
B
C
D
1302

Fig. 13

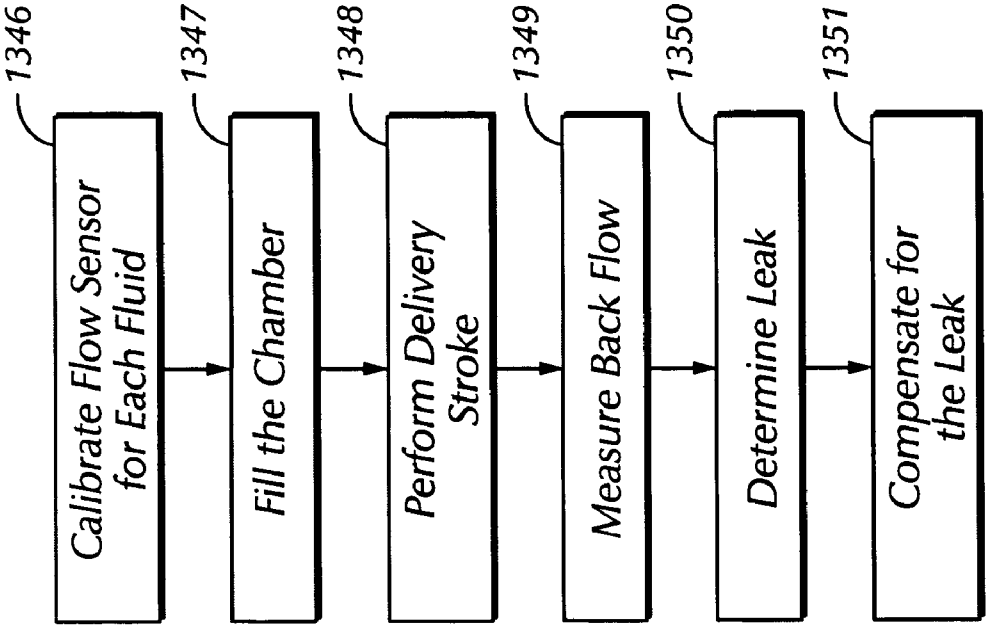

Fig. 13B

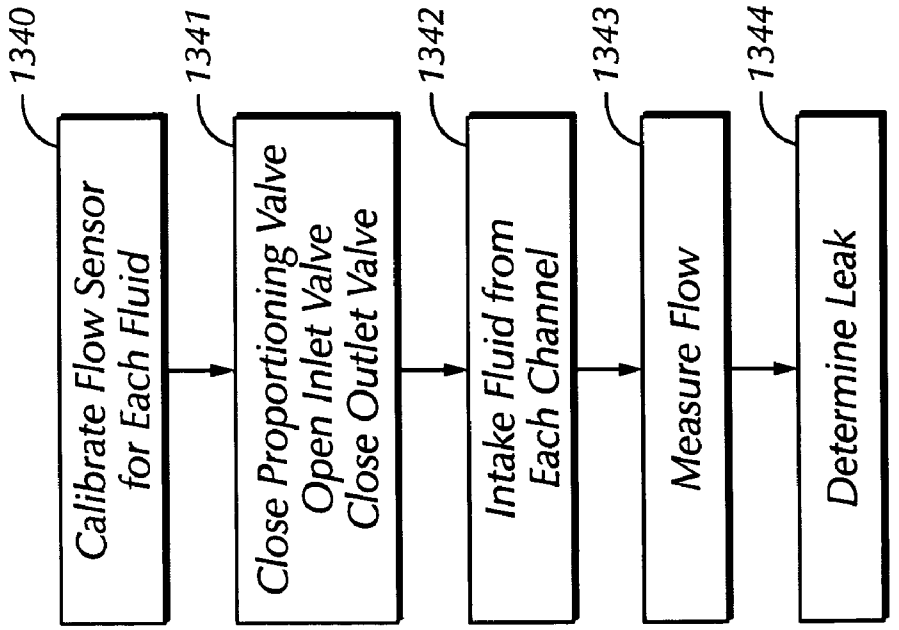

Fig. 13A

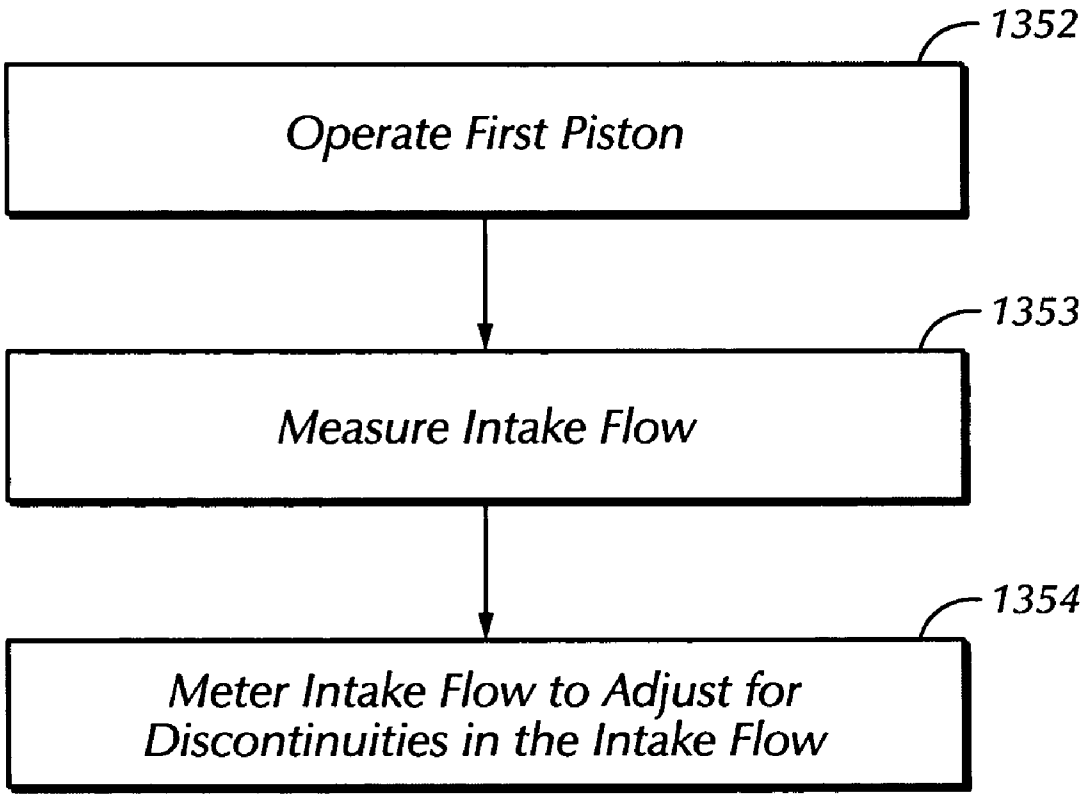
1352
Operate First Piston
1353
Measure Intake Flow
1354
Meter Intake Flow to Adjust for Discontinuities in the Intake Flow

Fig. 13C

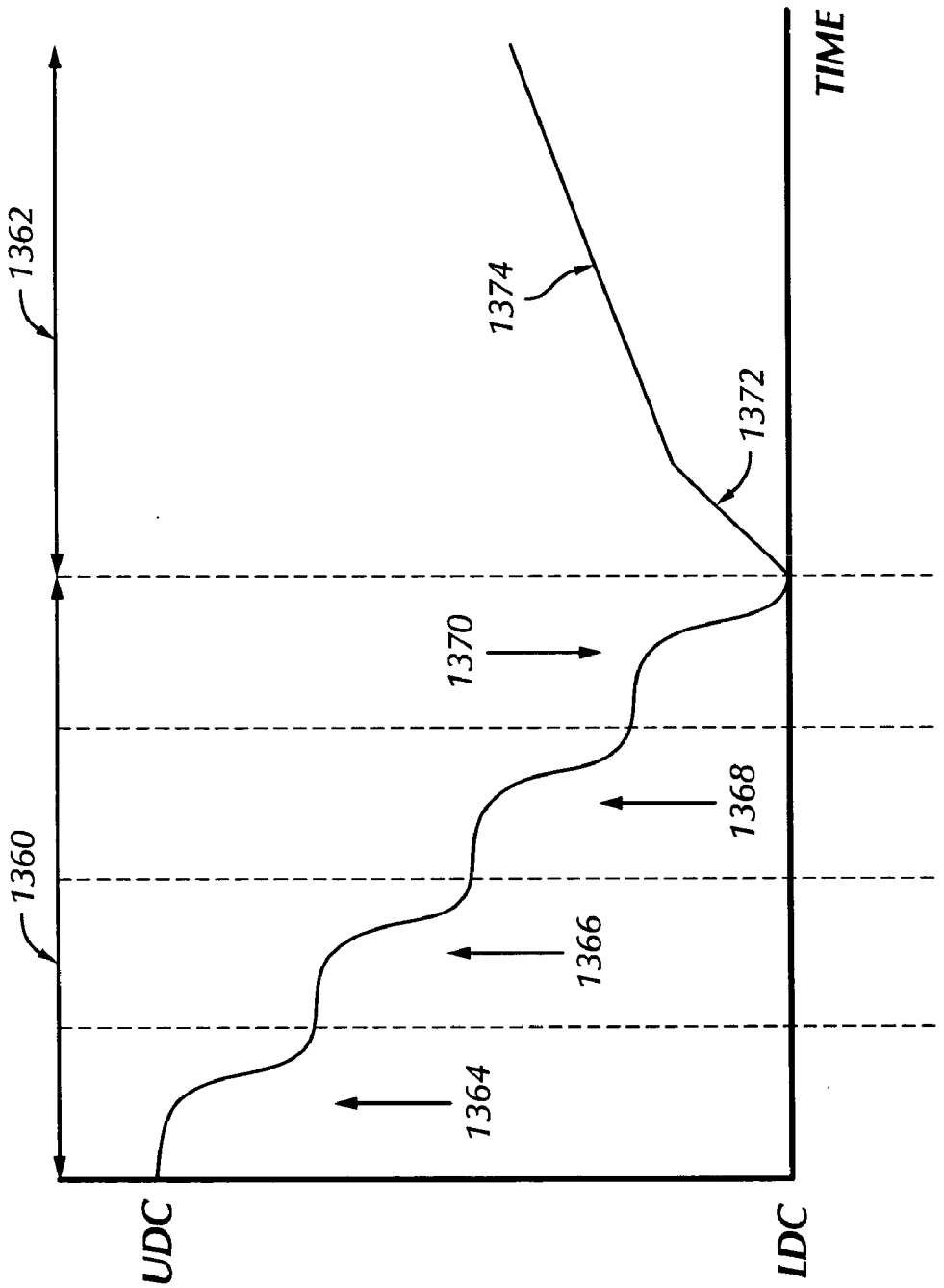

Fig. 13D

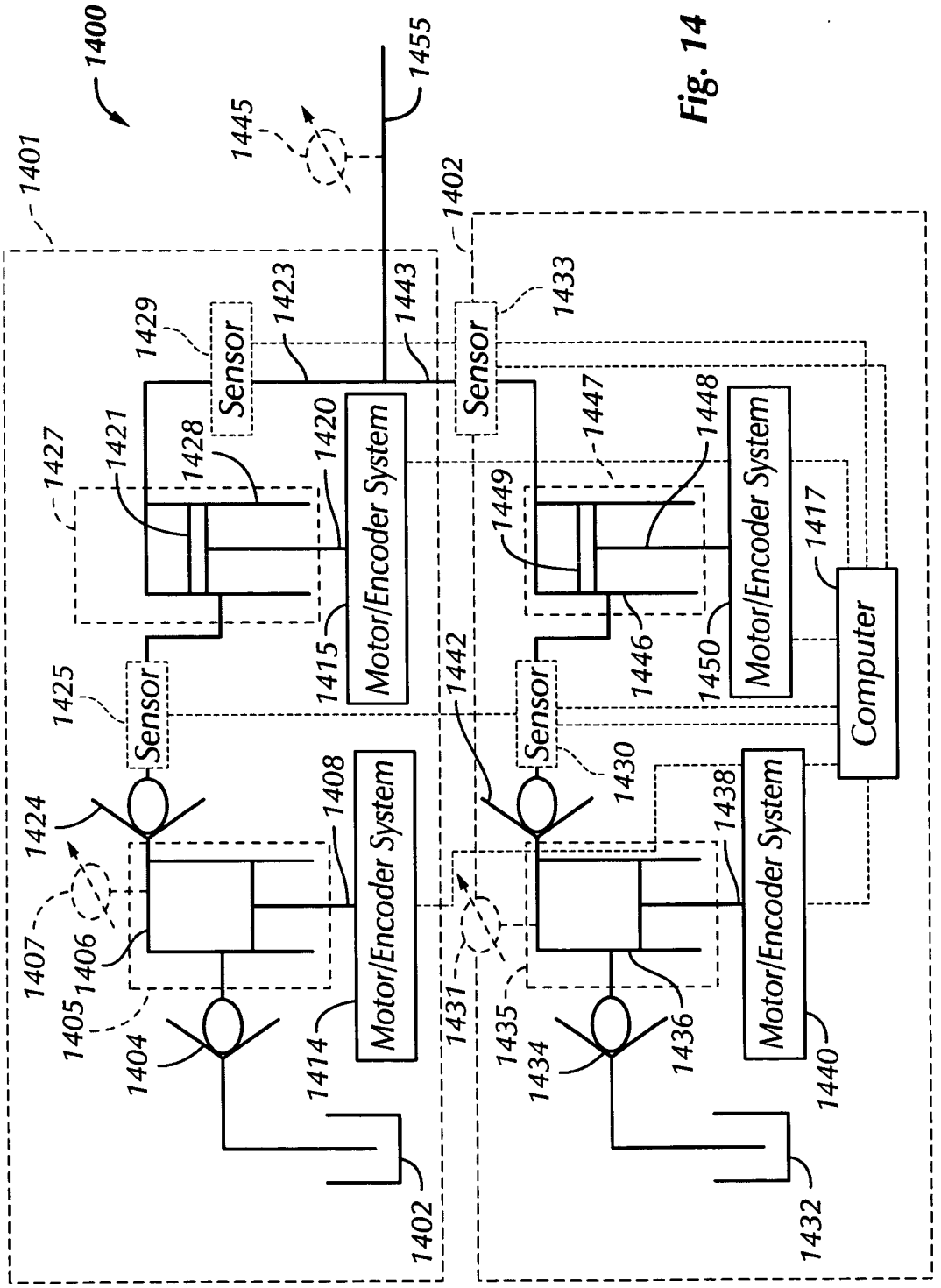
1400
1401
1402
1455
1445
1429
Sensor
1423
1443
1433
Sensor
1421
1428
1420
Motor/Encoder System
1427
1447
1448
1449
Motor/Encoder System
1417
Computer
1425
Sensor
1415
1442
Sensor
1446
1450
Motor/Encoder System
1424
1408
Motor/Encoder System
1430
1438
Motor/Encoder System
1407
1406
1405
1404
1414
1431
1435
1434
1436
1440
1402
1432

Fig. 14

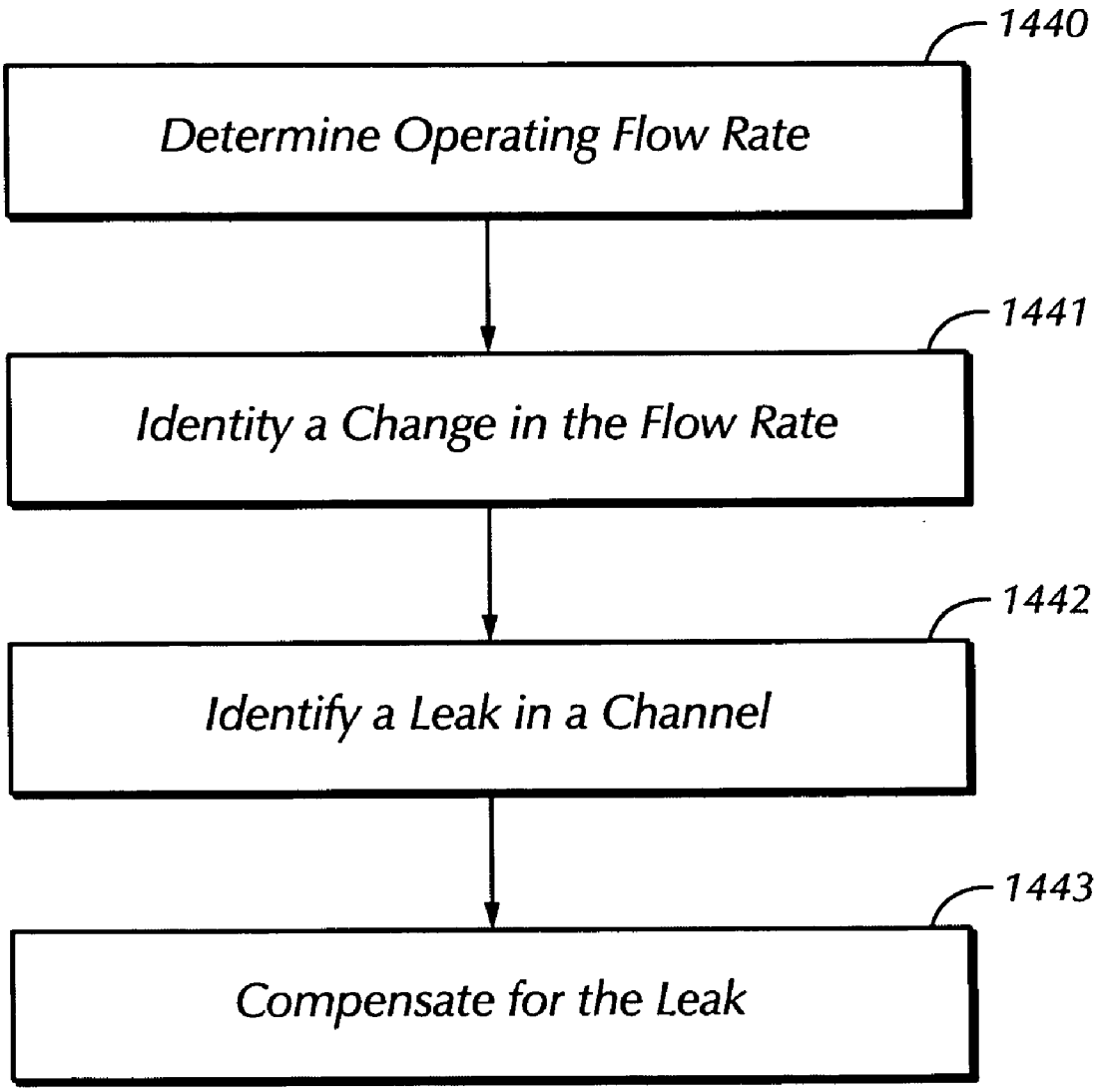
1440
Determine Operating Flow Rate
1441
Identity a Change in the Flow Rate
1442
Identify a Leak in a Channel
1443
Compensate for the Leak

Fig. 14A

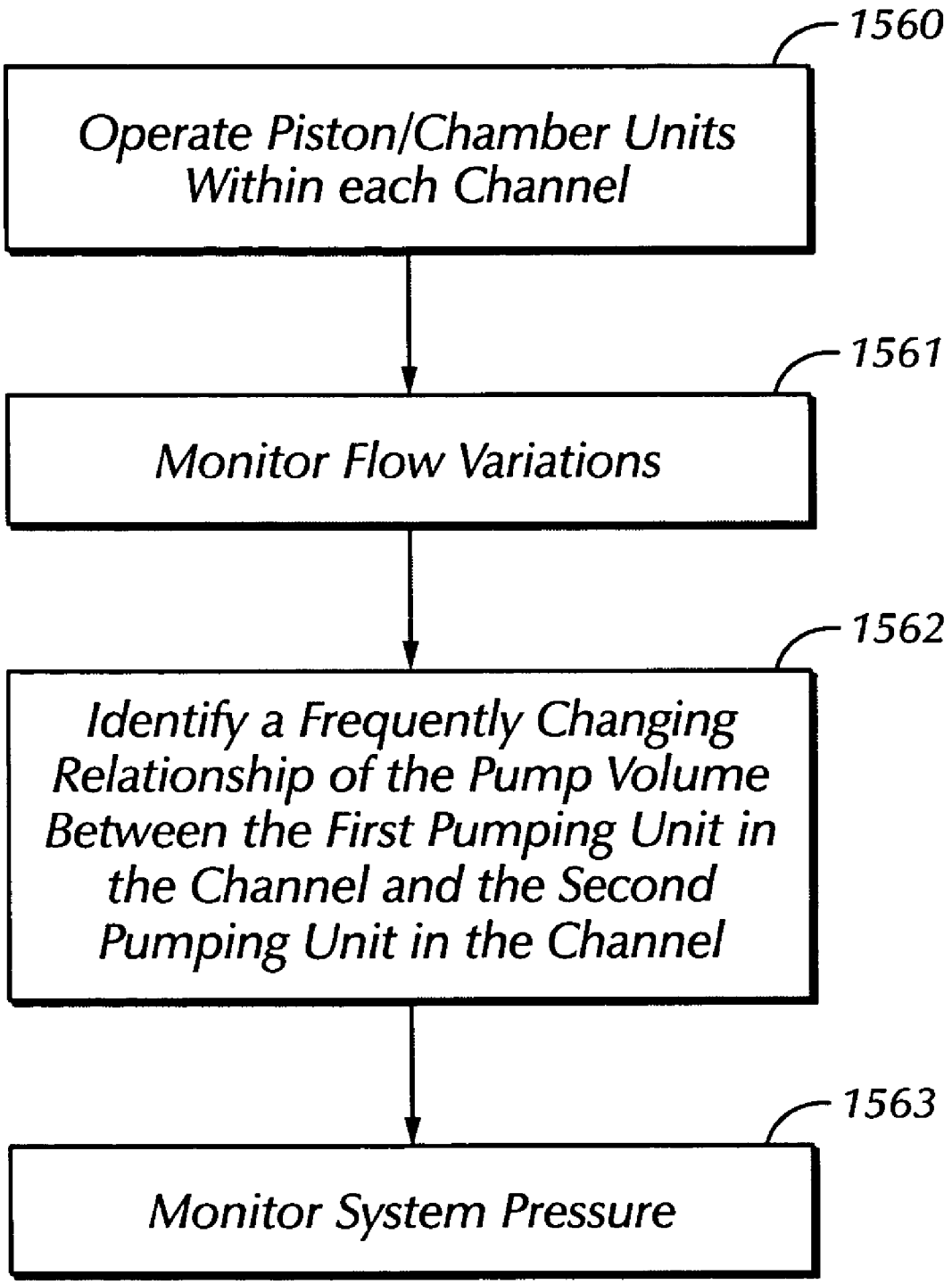
1560
Operate Piston/Chamber Units Within each Channel
1561
Monitor Flow Variations
1562
Identify a Frequently Changing Relationship of the Pump Volume Between the First Pumping Unit in the Channel and the Second Pumping Unit in the Channel
1563
Monitor System Pressure

Fig. 15A

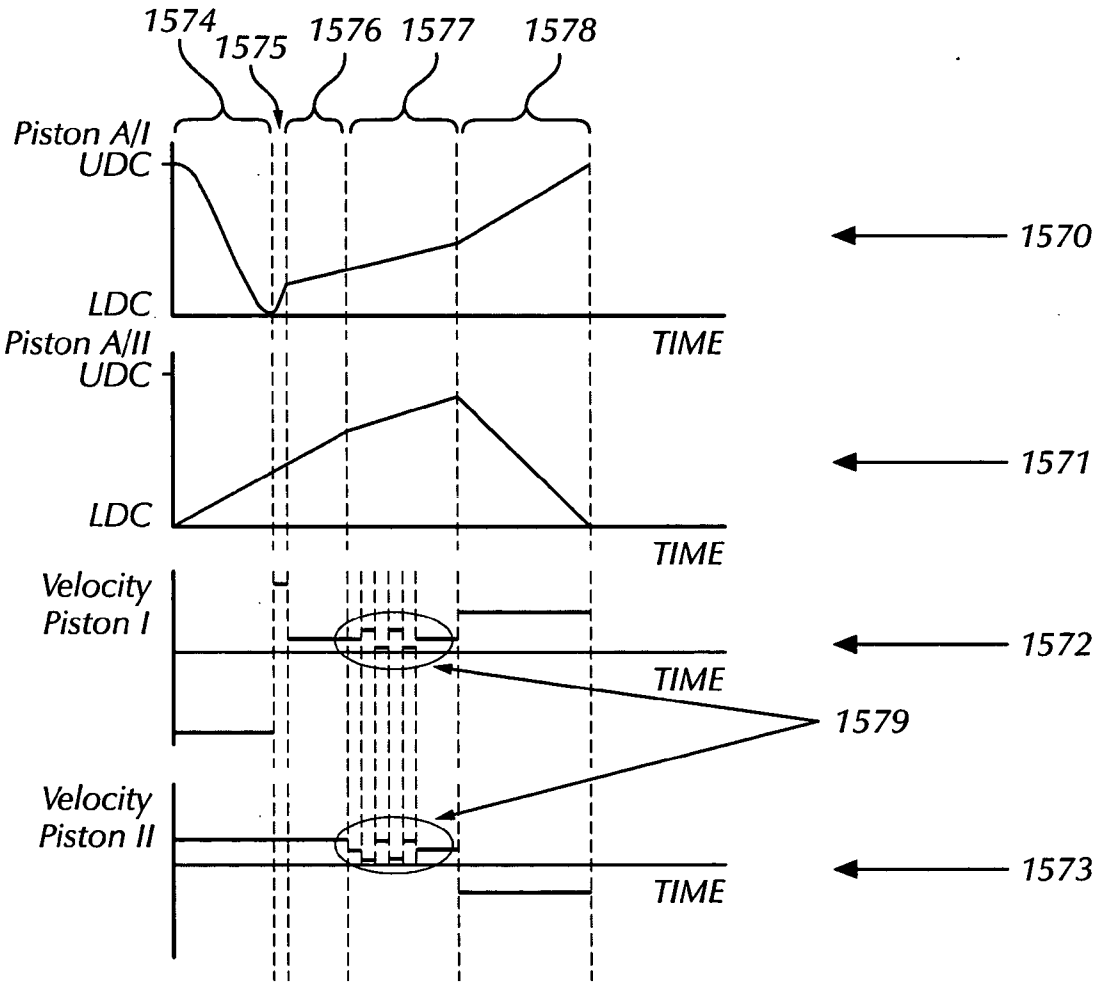
1574
1575
1576
1577
1578
Piston A/I
UDC
LDC
TIME
1570
Piston A/II
UDC
LDC
TIME
1571
Velocity
Piston I
TIME
1572
1579
Velocity
Piston II
TIME
1573

Fig. 15B

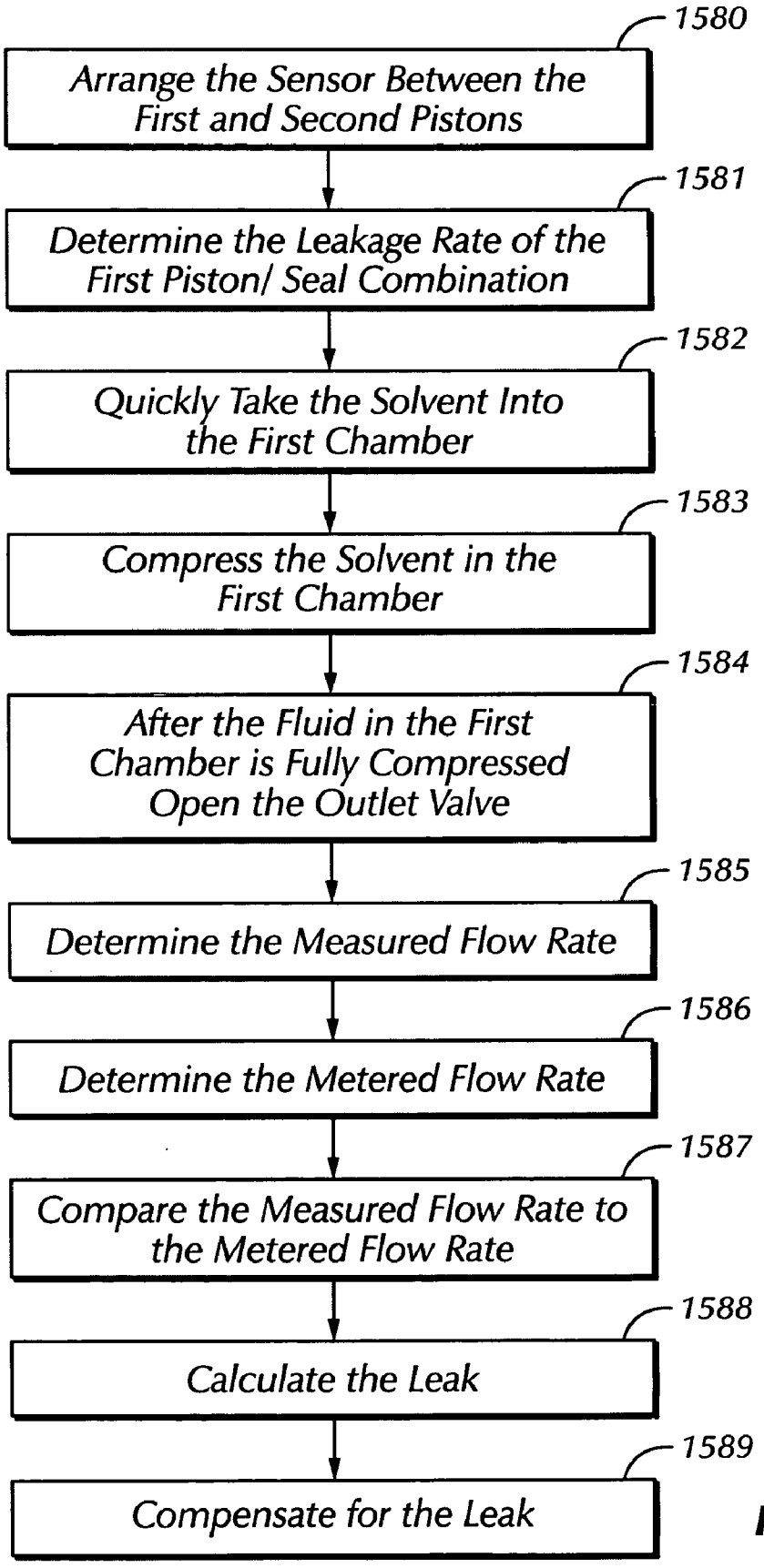
1580
Arrange the Sensor Between the First and Second Pistons
1581
Determine the Leakage Rate of the First Piston/ Seal Combination
1582
Quickly Take the Solvent Into the First Chamber
1583
Compress the Solvent in the First Chamber
1584
After the Fluid in the First Chamber is Fully Compressed Open the Outlet Valve
1585
Determine the Measured Flow Rate
1586
Determine the Metered Flow Rate
1587
Compare the Measured Flow Rate to the Metered Flow Rate
1588
Calculate the Leak
1589
Compensate for the Leak

Fig. 15C

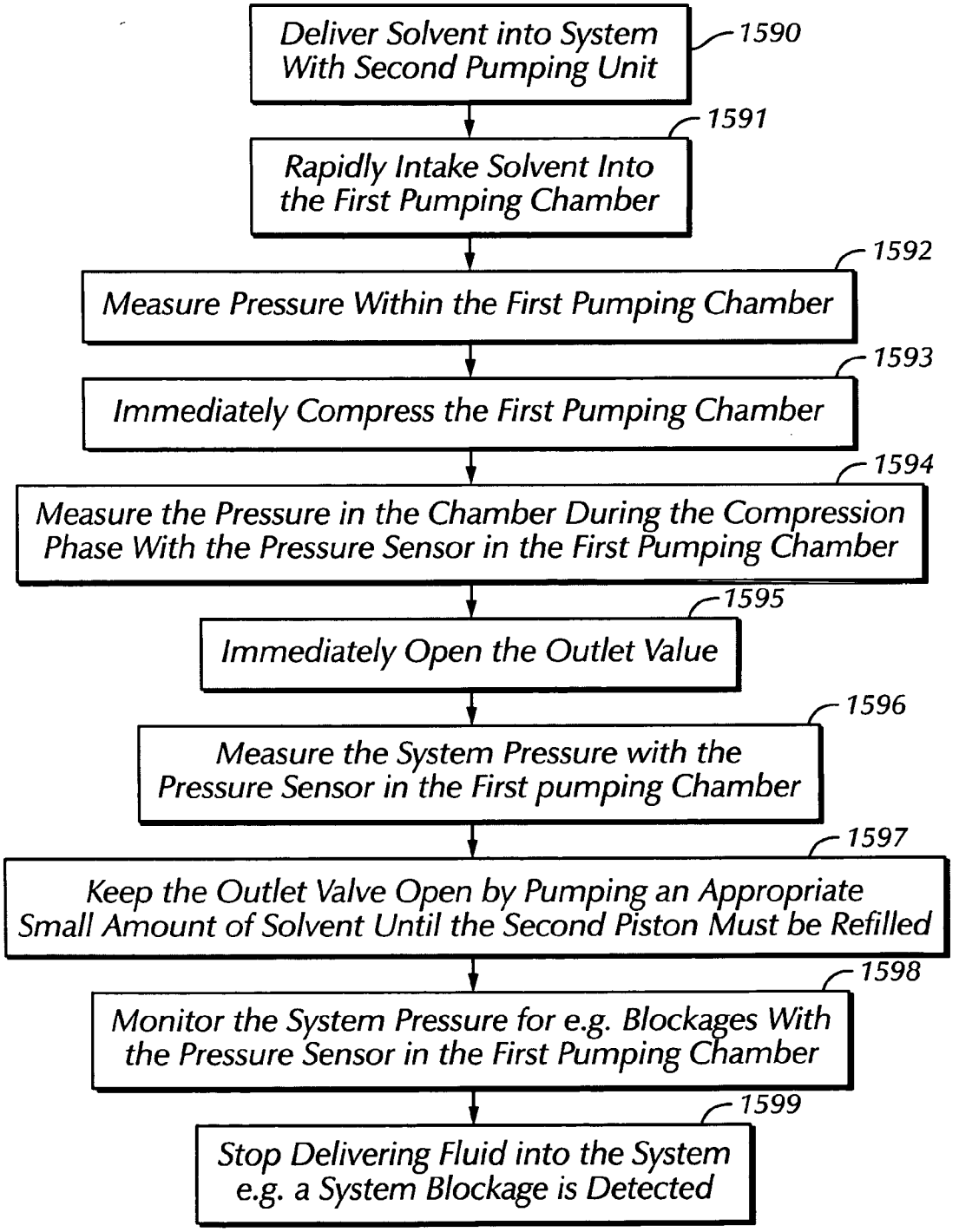
Deliver Solvent into System With Second Pumping Unit
1590
Rapidly Intake Solvent Into the First Pumping Chamber
1591
Measure Pressure Within the First Pumping Chamber
1592
Immediately Compress the First Pumping Chamber
1593
Measure the Pressure in the Chamber During the Compression Phase With the Pressure Sensor in the First Pumping Chamber
1594
Immediately Open the Outlet Value
1595
Measure the System Pressure with the Pressure Sensor in the First pumping Chamber
1596
Keep the Outlet Valve Open by Pumping an Appropriate Small Amount of Solvent Until the Second Piston Must be Refilled
1597
Monitor the System Pressure for e.g. Blockages With the Pressure Sensor in the First Pumping Chamber
1598
Stop Delivering Fluid into the System e.g. a System Blockage is Detected
1599

Fig. 15D

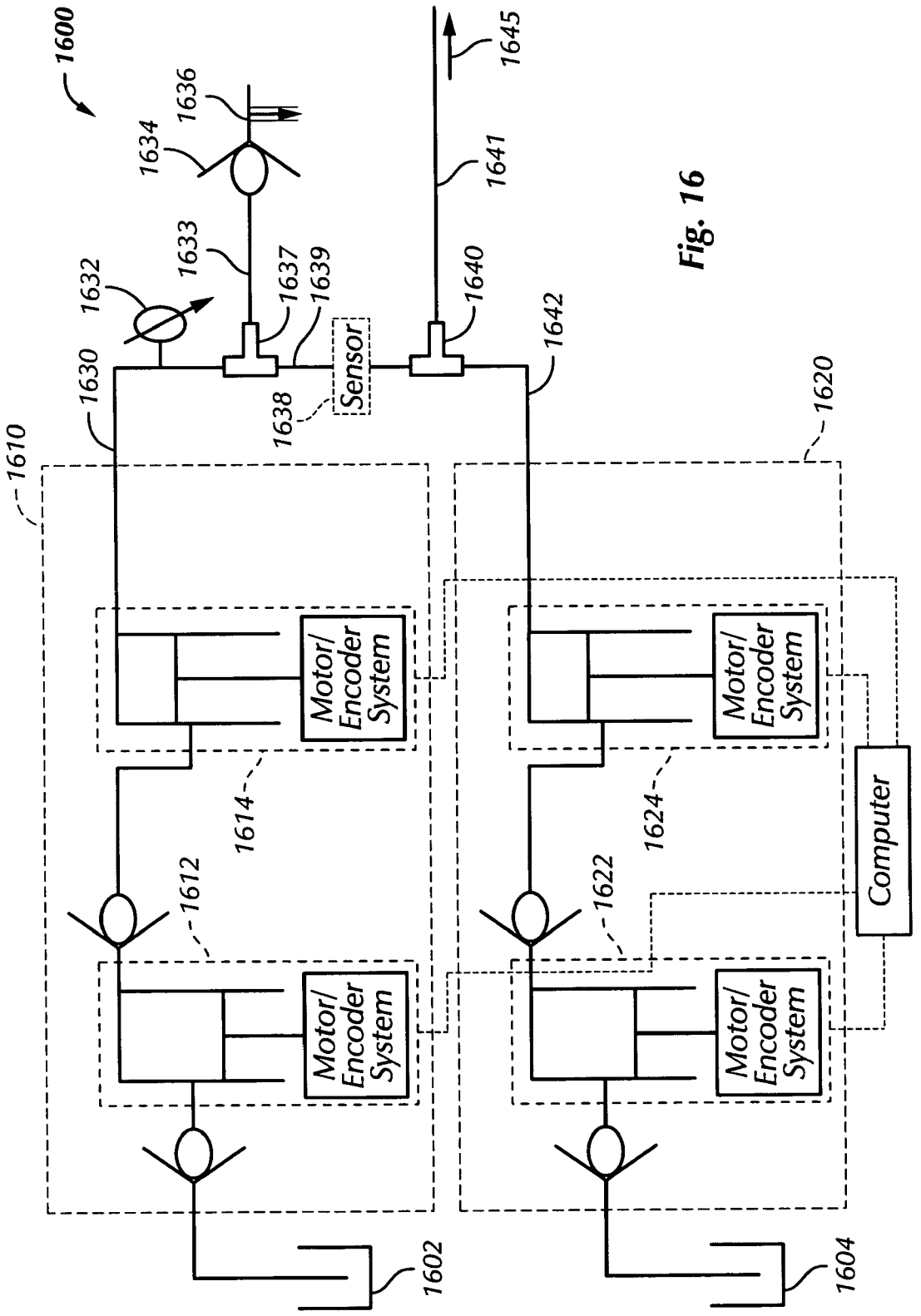
1600
1636
1634
1645
1641
1633
1632
1637
1639
1640
1642
1630
Sensor
1638
1610
1620
Motor/ Encoder System
Motor/ Encoder System
1614
1624
Computer
1612
1622
Motor/ Encoder System
Motor/ Encoder System
1602
1604

Fig. 16

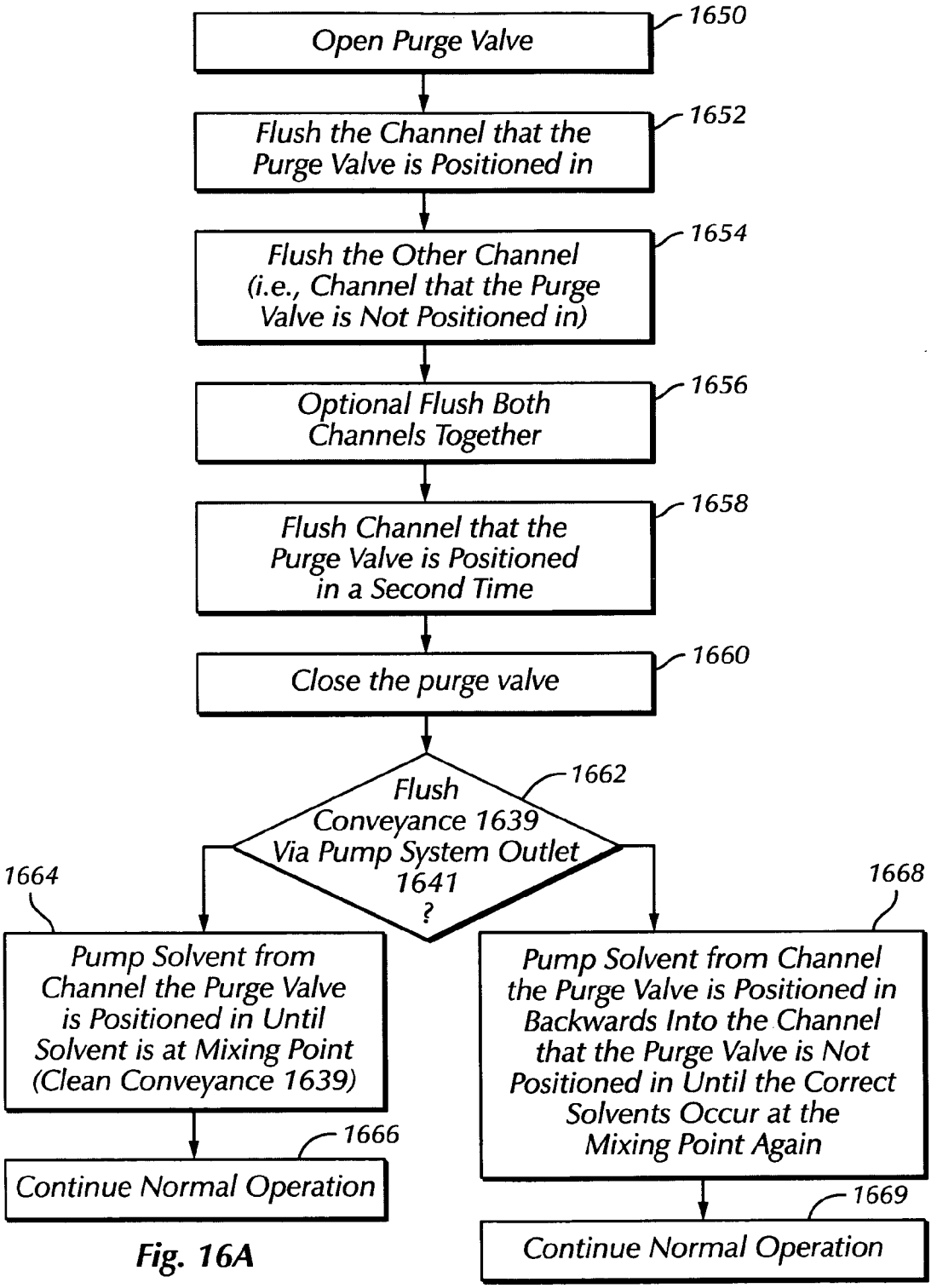
Open Purge Valve
1650
Flush the Channel that the Purge Valve is Positioned in
1652
Flush the Other Channel (i.e., Channel that the Purge Valve is Not Positioned in)
1654
Optional Flush Both Channels Together
1656
Flush Channel that the Purge Valve is Positioned in a Second Time
1658
Close the purge valve
1660
Flush Conveyance 1639 Via Pump System Outlet 1641 ?
1662
1664
Pump Solvent from Channel the Purge Valve is Positioned in Until Solvent is at Mixing Point (Clean Conveyance 1639)
1666
Continue Normal Operation
1668
Pump Solvent from Channel the Purge Valve is Positioned in Backwards Into the Channel that the Purge Valve is Not Positioned in Until the Correct Solvents Occur at the Mixing Point Again
1669
Continue Normal Operation

Fig. 16A

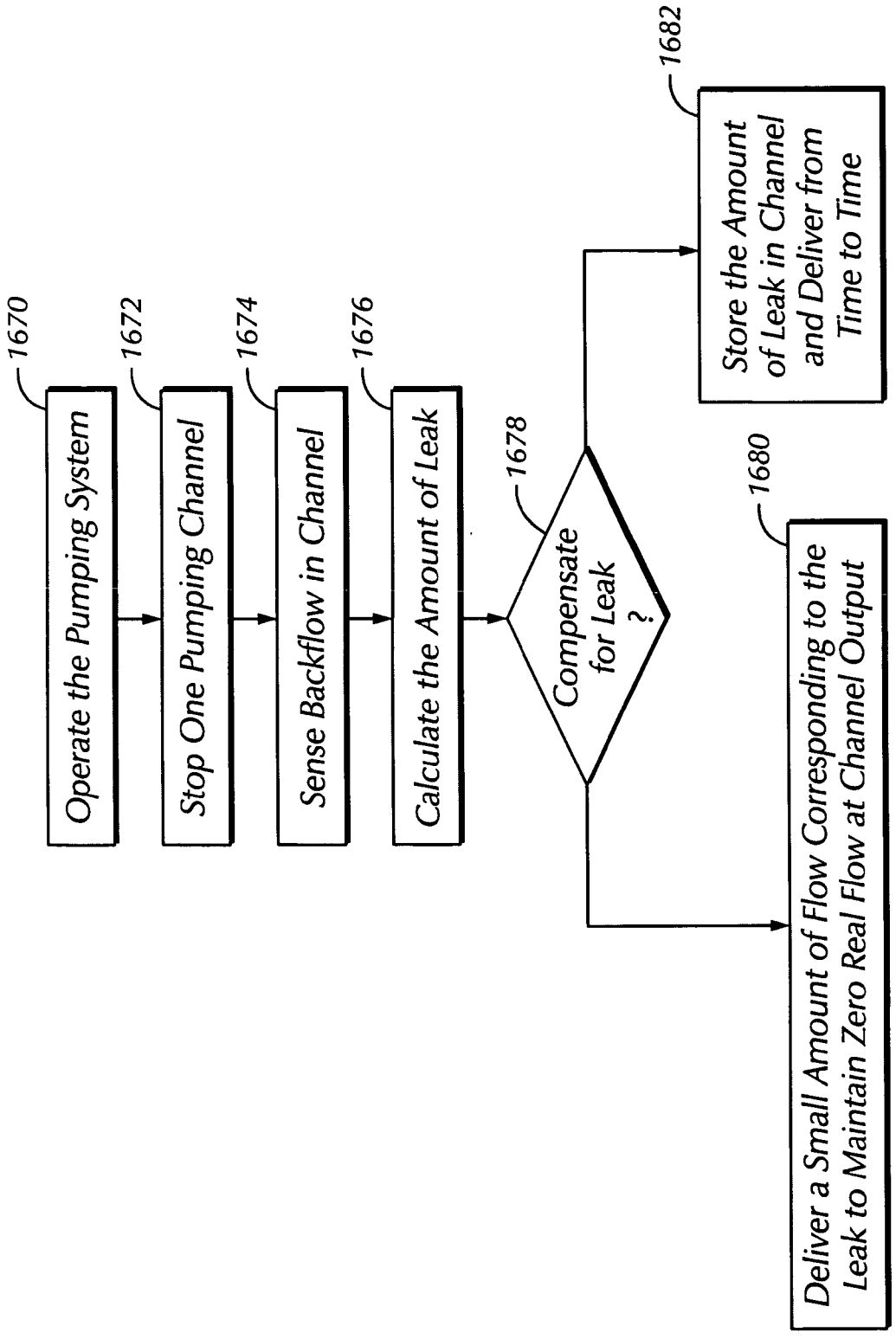
1670
Operate the Pumping System
1672
Stop One Pumping Channel
1674
Sense Backflow in Channel
1676
Calculate the Amount of Leak
1678
Compensate for Leak ?
1680
Deliver a Small Amount of Flow Corresponding to the Leak to Maintain Zero Real Flow at Channel Output
1682
Store the Amount of Leak in Channel and Deliver from Time to Time

Fig. 16B

CHROMATOGRAPHY SYSTEM WITH WASTE OUTPUT

[0001] This application claims priority from PCT Application No. PCT/EP2003/050794, filed on Nov. 5, 2003.

FIELD OF THE INVENTION

[0002] Chromatography systems perform a broad range of analysis methods to separate and/or analyze complex mixtures. There are a number of different types of chromatography systems, such as gas chromatography systems, Ion exchange chromatography systems, affinity chromatography systems, liquid chromatography systems, etc. In each type of chromatography system, components of a mixture are separated and distributed between two phases known as a mobile phase and a stationary phase.

DISCUSSION OF THE BACKGROUND ART

[0003] During operation, a mixture of various components is processed through a chromatography system at different rates. The different rates of migration through the chromatography system facilitate the separation of the mixture. Once the separation is accomplished, the different components of the mixture may be analyzed.

[0004] One conventional type of chromatography system is a High Pressure Liquid Chromatography system (HPLC). HPLC is a form of liquid chromatography used to separate compounds that are dissolved in a liquid. A conventional HPLC system is shown in FIG. **1**. A reservoir **100** stores a liquid. The liquid in the reservoir **100** is considered as the mobile phase. The liquid is drawn (i.e., pumped) out of the reservoir **100** using a pump **102**. A variety of pumps may be implemented, such as syringe pumps, reciprocating pumps, etc. A sample is introduced by an injector **104**. The mixture of the initial liquid held in the reservoir **100** and the sample is then pushed through a column **106** packed with material. The column **106** is known in the art as the stationary phase. Different components of the mixture move through the column **106** at different rates and as a result, may be analyzed by a detector **108**. Final analysis of the mixture is then performed using a computer **110**. The mixture ultimately is deposited as waste **112**.

[0005] A significant component of a chromatography system is the pumping system. A conventional pumping system includes at least one pump. The pump includes a chamber with a reciprocating piston disposed in the chamber. Each pump typically includes an input valve positioned at an input side of the chamber and an output valve positioned at an output side of the chamber. The input valve throttles the flow of liquid into the pump (i.e., chamber) and the outlet valve throttles the flow of liquid out of the pump (i.e., chamber).

[0006] One substantial feature that distinguishes the pumping systems is whether they are low-pressure gradient pumping systems or high-pressure gradient pumping systems in a low-pressure gradient pumping system, liquid mixing (i.e., mixing of the mobile phase if more than one solvent is used) occurs before the pump. In a high-pressure gradient pumping system, liquid mixing occurs after the liquid is processed through the pump.

[0007] Since a chromatography system separates and quantifies a sample (i.e., mixtures of compounds) based on the rate a liquid is processed through a column, controlling and managing the flow of liquid through the chromatography system is critical to performing the proper analysis of the sample (i.e., mixtures). A central component used to manage the flow of liquid through a chromatography system is the pumping system. In addition, since the liquid (i.e., flow rate, volume) that is processed through a chromatography system is extremely small, an incredible amount of precision and control must be applied to properly manage the flow of liquid through the chromatography system.

[0008] However, there are a number of problems that arise when processing liquid through the chromatography system. The problems impact the flow of liquid through the chromatography system and as a result, impact the analysis of the sample (i.e., mixtures of components). For example, varying the flow of liquid through a pump affects the analysis of the sample in a chromatography system; leaks may affect the flow of liquid through a chromatography system; incorrectly calibrated devices, such as sensor(s), may affect the flow of liquid through a chromatography system; cross over of liquids in a pumping system with multiple channels may affect the flow of liquid through a chromatography system; discontinuities in a liquid may affect the flow of liquid through a chromatography system; the intake operation of the pump may affect the flow of liquid through a chromatography system; and the piston timing of a pump may affect the flow of liquid through a chromatography system.

[0009] Thus, there is a need for a method and apparatus for managing the flow of liquids in a chromatography system. There is a need for a method and apparatus for managing the flow rate of liquids processed through a pumping system deployed in a chromatography system. There is a need for a method and apparatus for detecting and compensating for leaks within a pump. There is a need for a method and apparatus for attaining and retaining desired flow rates. There is a need for a method and apparatus for calibrating flow sensors. There is a need for a method and apparatus for avoiding channel cross over in multiple channel pumping systems. There is a need for a method and apparatus for optimizing delay volume in a pumping system. There is a need for a method and apparatus for optimizing the intake stroke in a pumping system. Lastly, there is a need for a pumping system with improved piston timing.

SUMMARY OF THE INVENTION

[0010] It is an object of the invention to provide an improved chromatography system. A variety of methods and apparatus for operating a pumping system are presented. Among these methods and apparatus are a pumping apparatus with a variable concept for flow generation dependent on a required flow rate; a method for determining and compensating for leaks in piston pumps; a method for calibrating a mass flow sensor; a method for avoiding channel cross flow in multiple channel pumping systems; a pumping method and apparatus with optimized delay volume; a pumping method and apparatus with optimized intake stroke; and a pumping method and apparatus with improved piston timing.

[0011] Embodiments of the invention can be partly or entirely embodied or supported by one or more suitable software programs, which can be stored on or otherwise provided by any kind of data carrier, and which might be executed in or by any suitable data processing unit.

[0012] One embodiment of a pumping system may comprise: means for configuring the pumping system with at least one sensor means; means for sensing a flow rate of fluid in the pumping system in response to configuring the pumping system with at least one sensor means; and means for determining leaks in the pumping system in response to sensing the flow rate of the fluid.

[0013] One embodiment of a pumping system may comprise: means for configuring the pumping system with at least one flow sensor; means for reconfiguring the at least one flow sensor within the pumping system; and means for determining leaks in the pumping system in response to reconfiguring the pumping system with the at least one flow sensor.

[0014] One embodiment of a pumping system may comprise: means for characterizing the pumping system to determine leaks in the pumping system; means for metering fluid through the flow sensor; and means for determining a calibration factor in response to characterizing the pumping system to determine leaks and in response to metering fluid through the flow sensor.

[0015] One embodiment of a pumping system may comprise: a pumping unit means; a flow sensor means positioned after the pumping unit means; means for characterizing the pumping unit means; means for metering fluid from the pumping unit means through the flow sensor means; and means for determining a calibration factor in response to metering fluid from the pumping unit means through the flow sensor means.

[0016] One embodiment of a pumping system may comprise: a channel; an output; means for pumping fluid at a flow rate in the pumping system; means for determining if the flow rate is below a predefined threshold; means for operating at least one first flow sensor at the output of the pumping system if the flow rate is below a predefined threshold; and means for determining if the flow rate is above the predefined threshold; and means for operating at least one second flow sensor within the channel if the flow rate is above the predefined threshold.

[0017] One embodiment of a pumping system may comprise: at least one channel, the channel including pumping units and an output; means for pumping fluid at a flow rate in the channel; means for determining if the flow rate is below a predefined threshold; means for operating at least one first flow sensor at the output of the channel if the flow rate is below a predefined threshold; and means for determining if the flow rate is above the predefined threshold; means for operating at least one second sensor within the channel if the flow rate is above the predefined threshold, wherein the at least one second flow sensor is positioned between the pumping units.

[0018] One embodiment of a pumping system may comprise: a conveyance; a pressure sensor coupled to the conveyance; a chamber coupled to the conveyance; means for compressing fluid in the chamber; means for monitoring pressure on the conveyance in response to compressing the fluid in the chamber; and means for determining a leak in response to monitoring the pressure on the conveyance.

[0019] One embodiment of a pumping system may comprise: a conveyance; a flow sensor coupled to the conveyance and to a valve, the valve further coupled to a chamber including a piston disposed therein, the chamber coupled to the conveyance; means for closing the valve; means for performing an intake stroke with the piston; means for monitoring for flow of fluid with the flow sensor in response to closing the valve and in response to performing an intake stroke with the piston; and means for determining a leak in response to monitoring for the flow of the fluid.

[0020] One embodiment of a pumping system may comprise: a pumping unit, the pumping unit comprising a chamber, and a pressure sensor coupled to the chamber; means for pressurizing the chamber; means for testing pressure in the chamber in response to pressurizing the chamber; means for determining a leak in response to testing the pressure in the chamber; and means for compensating for the leak in response to determining the leak.

[0021] One embodiment of a pumping system may comprise: an intake tube; a pressure sensor coupled to the intake tube and a chamber coupled to the intake tube; means for filling the chamber with fluid by conveying fluid through the intake tube; means for monitoring pressure on the intake tube in response to conveying fluid on the intake tube; and means for determining if the pressure has dropped below a predefined level in response to monitoring pressure on the intake tube.

[0022] One embodiment of a pumping system may comprise: an intake tube; a conveyance; a switching valve coupling the intake tube to the conveyance; a flow sensor coupled to the conveyance and a chamber, the chamber including a piston disposed therein; means for closing the switching valve; means for attempting to convey fluid on the conveyance subsequent to closing the switching valve; means for measuring fluid flow with the flow sensor in response to attempting to convey the fluid on the conveyance; and means for determining a leak in response to measuring the fluid flow with the flow sensor.

[0023] One embodiment of a pumping system may comprise: a chamber including an outlet and a piston disposed therein; an outlet valve coupled to the outlet of the chamber; a flow sensor coupled to the outlet valve; means for closing the outlet valve; means for moving the piston upward in the chamber; means for measuring fluid flow with the flow sensor in response to moving the piston upward in the chamber; and means for determining a leak in response to measuring the fluid flow with the flow sensor.

[0024] One embodiment of a pumping system may comprise: a conveyance coupled to a pumping unit; means for conveying fluid on the conveyance, the fluid including discontinuities; and means for operating the pumping unit to limit the discontinuities in the fluid.

[0025] One embodiment of a pumping system may comprise: means for metering at a flow rate; means for determining a leak in response to metering at the flow rate; and means for compensating for the leak by metering at a new flow rate.

[0026] One embodiment of a pumping system may comprise: means for monitoring the pumping system with a flow sensor; means for determining a change in flow rate in response to monitoring the pumping system with the flow sensor; and means for identifying a leak in response to determining a change in the flow rate.

[0027] One embodiment of a pumping system may comprise: means for monitoring a flow rate; means for determining a leak rate in response to monitoring the flow rate; and means for compensating for the leak rate in response to determining the leak rate.

[0028] One embodiment of a pumping system may comprise: means for monitoring a flow rate; means for determining a leak rate in response to monitoring the flow rate; and means for adjusting the flow rate in response to determining the leak rate.

[0029] One embodiment of a pumping system may comprise: a first pumping unit capable of generating a first volume of fluid and a second pumping unit capable of generating a second volume of fluid, wherein the first volume of fluid has a relationship with the second volume of fluid; means for operating the first pumping unit; means for operating the second pumping unit; means for identifying a change in the relationship between the first volume of fluid and the second volume of fluid in response to operating the first pumping unit and in response to operating the second pumping unit; and means for identifying a leak in response to identifying the change in the relationship between the first volume of fluid and the second volume of fluid.

[0030] One embodiment of a pumping system may comprise: first and second pumping units coupled together and a flow sensor located between the first and second pumping units; means for metering a flow rate; means for measuring a flow rate; means for comparing the measured flow rate to the metered flow rate; and means for determining a leak in response to comparing the measured flow rate to the metered flow rate.

[0031] One embodiment of a pumping system may comprise: a first pumping unit comprising a first chamber, a pressure sensor coupled to the first chamber; a second pumping unit including a second chamber, the second pumping unit in series with the first pumping unit; a valve positioned between the first pumping unit and the second pumping unit; means for delivering solvent with the second pumping unit; means for intaking solvent into the first chamber; means for compressing the solvent in the first chamber; means for opening the outlet valve in response to compressing the solvent in the first chamber while the second pumping unit is delivering solvent; means for delivering a small amount of solvent with the first pumping unit until the second pumping unit must be refilled; and means for measuring system pressure in response to delivering solvent with the first pumping unit and opening the outlet valve.

[0032] One embodiment of a pumping system may comprise: a first channel transporting first fluid; a second channel transporting second fluid; a waste output having a valve coupled to the first channel and coupled to the second channel via a conveyance, the waste output adapted for transporting waste, a system output coupled to the first channel via the conveyance and coupled to the second channel, the system output adapted for transporting system fluid; means for opening the valve; means for flushing the second channel in response to opening the valve; means for flushing the first channel in response to flushing the second channel; means for closing the valve in response to flushing the first channel; and means for pumping solvent from the first channel through the conveyance.

[0033] One embodiment of a pumping system may comprise: a first channel pumping first fluid; a second channel pumping second fluid; a system output coupled to the first channel and coupled to the second channel, the system output transporting system fluid in response to the first fluid and in response to the second fluid and a flow sensor coupled to the output of the first channel to measure the flow of the first fluid; means for stopping the first channel pumping the first fluid; means for sensing backflow with the flow sensor in response to stopping the first channel pumping the first fluid; and means for determine a leak in response to sensing the backflow.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] FIG. **1** displays a block diagram of a prior art chromatography system.

[0035] FIG. **2** displays a block diagram of an embodiment of an isocratic pumping system with additional liquid selection.

[0036] FIG. **3** displays a block diagram of an embodiment of a pump control chip.

[0037] FIG. **4** displays a block diagram of an embodiment of a computer.

[0038] FIG. **5** displays a block diagram of an embodiment of a high-pressure gradient pumping system.

[0039] FIG. **6** displays a block diagram of an embodiment of a low-pressure gradient pumping system.

[0040] FIG. **7** displays a block diagram of an embodiment of a high-pressure gradient pumping system.

[0041] FIG. **8** displays a block diagram of an embodiment of a high-pressure gradient pumping system.

[0042] FIG. **9**A displays a schematic diagram of a pumping system, such as a single-channel pumping system, where the pumping units are positioned in series.

[0043] FIG. **9**B displays a schematic diagram of a channel of a pumping system with pumping units configured in parallel.

[0044] FIG. **10** displays a schematic diagram of a high-pressure gradient pumping system, such as a dual-channel pumping system.

[0045] FIG. **11**A displays a flow diagram depicting a method of determining leaks in a pumping system.

[0046] FIG. **11**B displays a flow diagram depicting a method of reconfiguring sensors in a pumping system.

[0047] FIG. **11**C displays a flow diagram depicting a method of calibrating sensors.

[0048] FIG. **11**D displays a graph of voltage versus flow rate.

[0049] FIG. **11**E displays a flowchart depicting a method of producing a variable flow rate.

[0050] FIG. **12** displays a schematic of a pumping unit including a flow sensor and a pressure sensor(s).

[0051] FIG. **12**A displays a method of identifying and compensating for leaks using a pressure sensor.

[0052] FIG. **12**B displays a method of identifying and compensating for leaks using a flow sensor.

[0053] FIG. **12**C displays a method of identifying and compensating for leaks using a pressure sensor.

[0054] FIG. **12**D displays a method of identifying a blocked inlet tube.

[0055] FIG. **12**E displays a method of identifying and compensating for leaks using a pressure sensor.

[0056] FIG. **12**F displays a flow diagram that depicts a method of detecting a leak in a proportioning valve.

[0057] FIG. **12**G displays a flow diagram that depicts a method of testing the tightness of a proportioning valve.

[0058] FIG. **13** displays a schematic of a single-channel pumping system including flow sensors.

[0059] FIG. **13**A displays an embodiment of a flow diagram depicting a method of detecting a leak in a gradient valve.

[0060] FIG. **13**B displays an embodiment of a flow diagram depicting a method of detecting a leak in an inlet valve.

[0061] FIG. **13**C displays a flow diagram of a method of performing a smooth intake stroke.

[0062] FIG. **13**D displays a graph depicting a method of metering the intake flow to adjust for discontinuities in the intake flow.

[0063] FIG. **14** displays a dual-channel pumping system including flow sensors.

[0064] FIG. **14**A displays a flow diagram depicting a method of operating a pumping system.

[0065] FIG. **15**A displays a flow diagram depicting a method of determining a leak in a piston.

[0066] FIG. **15**B displays a graph depicting the flow variations within a channel.

[0067] FIG. **15**C displays a flow diagram depicting a method of determining the piston velocity required to produce the nominal (desired) flow rate.

[0068] FIG. **15**D displays a flow diagram depicting a method of monitoring compression phases in a pumping chamber and monitoring the system pressure of a chromatography system.

[0069] FIG. **16** displays a schematic of a dual-channel pumping system including a flow sensor and a pressure sensor.

[0070] FIG. **16**A displays a flowchart depicting a method of flushing a multi-channel pumping system.

[0071] FIG. **16**B displays a flowchart depicting a method of eliminating cross-channel flow in a multi-channel pumping system.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0072] While the present invention is described herein with reference to illustrative embodiments for particular applications, it should be understood that the invention is not limited thereto. Those having ordinary skill in the art and access to the teachings provided herein will recognize additional modifications, applications, and embodiments within the scope thereof and additional fields in which the present invention would be of significant utility.

[0073] FIG. **2** displays a block diagram of an embodiment of an isocratic pumping system with additional liquid selection at a pump inlet. It should be appreciated that the methods presented in the instant application may be implemented on a pumping system, such as a pumping system **200** displayed in FIG. **2**. The pumping system **200** displays two pumping units **218** and **232** positioned in series. Pumping unit **218** includes an inlet valve **216** on an input side of pumping unit **218** and an outlet valve **220** on an output side of the pumping unit **218**. Pumping unit **232** includes a purge valve **242** on an output side of the pumping unit **232**.

[0074] A liquid reservoir **202** stores liquids denoted as A, B, C, and D. Input conveyance **204**, **206**, **208**, and **210** provide a pathway and convey liquid A, B, C, or D from the liquid reservoir **202** to a liquid selection valve **212**. A selector **214** selects which input conveyance (**204**, **206**, **208**, **210**) is connected to the inlet valve **216**. The liquid selection valve **212** is controlled by a liquid selection unit **294**. It should be appreciated that in another embodiment of the present invention, a low-pressure gradient pumping system may be implemented by implementing the liquid selection valve **212** as a proportioning valve and implementing the liquid selection unit **294** as a gradient control unit.

[0075] A pumping unit **218** is shown. The pumping unit **218** includes a chamber **222**, a piston **224**, a seal **226**, and a piston holder **228**. Liquid A, B, C, or D is each drawn through an inlet valve **216** into the chamber **222** by a downward motion (i.e., intake stroke) of the piston **224**. An outlet valve **220** throttles a pathway to a damper unit **230**. It should be appreciated that while the damper unit **230** and a pressure transducer **284** are shown in pumping system **200**, either the damper unit **230** and/or the pressure transducer **284** may be removed.

[0076] Liquid A, B, C, or D flows through the damper unit **230** to a pumping unit **232**. The pumping unit **232** includes a chamber **234**, a piston **236**, a seal **238**, and a piston holder **240**. The piston **236** performs an intake stroke and draws liquid A, B, C, or D into the chamber **234**. On a delivery stroke (i.e., upward movement) of the piston **236**, liquid A, B, C, or D leaves the chamber **234** and is pushed through a valve, such as a purge valve **242**. The purge valve **242** provides a pathway **244** to the system or a pathway **246** to waste. It should be appreciated that throughout the disclosure, while a specific pumping unit (i.e., **218**, **232**) may be described and discussed, various modifications of the pumping unit (i.e., **218**, **232**) may be performed and still remain within the scope of the present invention. In addition, while pumping units with chambers and pistons are implemented, other types of pumping units, such as pumping units with impellers, etc., are anticipated and are within the scope of the present invention. In addition, valves, such as inlet valves **216**, outlet valve **220**, or purge valve **242**, may be implemented as active valves or passive valves.

[0077] In one embodiment, a gear system **248** includes a ball **250**, an actuator **252**, a shaft **254**, a gear **256**, and a gear **258**. The ball **250** is housed in the actuator **252** and is in contact with the piston holder **228**. The shaft **254** causes the ball **250** and the piston **224** to move upward (i.e., delivery

stroke) and downward (i.e., intake stroke), as the gear **256** is rotated clockwise and then counterclockwise. In one embodiment, the gear **256** is a toothed gear, which is interlocked with a gear **258**, which is connected to a motor/encoder unit **260**. In one embodiment, a motor/encoder unit **260** is a unit that includes a combined motor and encoder coupled to the motor. A position-servo unit **299** communicates information to the motor/encoder unit **260** through a position-servo interface **264** and receives feedback as shown by **262**.

[**0078**] A gear system **266** includes a ball **268** positioned within an actuator **270** and makes contact with the piston holder **240**. A shaft **272** causes the ball **268** and the piston **236** to reciprocate in an upward and downward motion as a gear **274** is rotated in the clockwise and counterclockwise direction. The gear **274** is interlocked with a gear **276**, which is connected to a motor/encoder unit **278**. A position-servo unit **297** communicates information to the motor/encoder unit **278** through a position-servo interface **282** and receives feedback as shown by **280**.

[**0079**] In one embodiment, a pump control chip **288** is implemented to control the pumping system **200**. A position-servo unit **299** is controlled by a pump drive control unit **298**. The position-servo unit **299** controls the motor/encoder unit **260** through the position-servo interface **264** and receives feedback through a feedback **262**. The position-servo unit **297** controls the motor/encoder unit **278** through a position-servo interface **282** and receives feedback on the position and movement of the motor/encoder unit **278** through a feedback **280**.

[**0080**] The pump drive control unit **296** and the pump drive control unit **298** interface with an analog-to-digital converter (ADC) **290**, an inlet control unit **292**, and a liquid selection unit **294** through a system controller **295**. In addition, end users may use a user interface **286** to interface with the pumping system **200** through the system controller **295**.

[**0081**] The ADC **290** interfaces and controls a pressure transducer **284**, an inlet control unit **292** interfaces and controls the inlet valve **216**, and the liquid selection unit **294** interfaces and controls the liquid selection valve **212**. A more thorough explanation of the operation of the pumping system **200** may be found in European Patent EP0309596, entitled "Pumping apparatus for delivering liquid at high pressure," published Apr. 5, 1989, which is herein incorporated by reference.

[**0082**] During operation, one of the liquid containers A, B, C, or D, shown collectively as liquid reservoir **202**, is connected to the inlet valve **216** so that liquid A, B, C, or D can be delivered. This can be accomplished by either holding the selector **214** in a fixed position so that the liquid selection valve **212** is connected to one of the liquid containers A, B, C, or D in the liquid reservoir **202**. Alternatively, the liquid selection valve **212** may be operated as a proportioning valve by moving the selector **214** across each input conveyance **204**, **206**, **208**, and **210** so that one of the liquid containers A, B, C, or D proportions the amount of liquid A, B, C, or D drawn in from the liquid reservoir **202**.

[**0083**] During a start-up period, the piston **224** is moved to a predefined distance referred to as the upper dead center (UDC). Under the control of the pump control chip **288**, the piston **224** moves upward into the chamber **222** until the piston holder **228** abuts the lower end of the chamber **222**. Once this end position has been reached, the piston **224** moves back downward a predefined distance. In addition, the corresponding angular setting of the motor/encoder unit **260** is registered and stored to recreate the movement of the piston **224** to the UDC position. In one embodiment, moving a piston, such as piston **224**, to a predefined position based on the corresponding angular setting of the motor/encoder unit **260** is referred to as metering. In another embodiment of the present invention, any change of piston position or rate of motion, which results in a change in the flow rate of liquid entering and exiting a chamber, such as chamber **222**, is considered metering. Metering may be performed by operating the piston **224** in combination with the motor/encoder unit **260** and the pump control chip **288**. A similar procedure may be performed to record a piston position where the piston **224** moves to the lowest point in the chamber **222** required to draw liquid A, B, C, or D into the chamber **222**. The lowest point is known as the lower dead center (LDC).

[**0084**] After identifying and setting the UDC position and the LDC position in both pumping units **218** and **232**, the pumping system **200** begins nominal operation. The inlet valve **216** is opened under the control of the inlet control unit **292** and the piston **224** moves down from the UDC position to the LDC position. As the piston **224** moves from the UDC position to the LDC position, liquid A, B, C, or D is drawn into the chamber **222**.

[**0085**] In one embodiment, an end user operates the position-servo interface **282** to specify a flow rate for the pumping system **200**. A corresponding stroke length, which is defined as the distance the piston **224** travels between the UDC position and the LDC position, is then implemented in both pumping units **218** and **232** to accomplish the flow rate. Based on the flow rate input by the end user, the pump control chip **288** computes a corresponding stroke length using a predetermined mathematical relationship between flow rate and stroke length (or stroke volume, which is proportional to the stroke length). In an alternate embodiment of the present invention, the pump control chip **288** may be modified to permit a variable or changing selection of the stroke length or volume.

[**0086**] Once the piston **224** has traveled the stroke length determined by the pump control chip **288** from the UDC position to the LDC position, the motor/encoder unit **260** stops movement to stop the flow of liquid into the chamber **222** and the inlet valve **216** is closed. The motor/encoder unit **260** is restarted, moving in the opposite direction as before until it again reaches the UDC position. Once this is completed, the sequence repeats with the piston **224** reciprocating in the chamber **222** (i.e., moving down from the UDC position to the LDC position and back again). The piston **236** performs a similar sequence of motions and delivers liquid A, B, C, or D to other parts of the chromatography system (i.e., column) as shown by the pathway **244**. In one embodiment of the present invention, the movement of piston **224** and piston **236** are synchronized in such a way that the flow through the system is constant over time.

[**0087**] FIG. **3** displays a block diagram of a pump control chip. In one embodiment, pump control chip **300** represents an implementation of the pump control chip shown as **288**

of FIG. **2**. In another embodiment, the pump control chip **300** is implemented in a pumping system. In another embodiment, the pump control chip **300** may be implemented in a computer that interfaces with a pumping system. Input signaling, such as control signals **302**, address signals **304**, and range detector signals **306**, are received in a bi-directional bus interface **308**. The bi-directional bus interface **308** provides an interface between the input signaling (i.e., **302**, **304**, and **306**) and a frequency synthesizer unit **310**, a compensation position unit **312**, and a range detector unit **314**. The frequency synthesizer unit **310** provides frequency and counting direction information based on the movement of a piston. The compensation position unit **312** calculates the amount of piston movement necessary in the pre-compression phase of piston operation. The range detector unit **314** defines the upper dead center (UDC) and lower dead center (LDC) of the piston and is responsible for defining the total stroke length of a piston. The set point position counter **316** maintains the position of the piston. For example, if a piston reaches the UDC or LDC, a signal is sent to the set point position counter **316**, the number of steps for pre-compression are transferred to the set point position counter **316** as soon as the piston begins to move upwards, etc.

[**0088**] The range detector unit **314** provides input to an inlet valve control unit **318**, which controls an active valve **324**. The range detector unit **314** and the set point position counter **316** provide input to a position-servo system **320**, which interfaces with a motor **328** through a position-servo interface **326**. The motor **328** is coupled to an encoder **330**, which provides feedback to the position-servo system **320**. Lastly, the set point position counter **316**, the range detector unit **314**, and the bi-directional bus interface **308** provide input to the gradient valve timer **322**, which provides an output to the gradient valve as shown by **332**. It should be appreciated that while a specific embodiment of a pump control chip **300** is displayed and discussed, a variety of embodiments may be implemented and still remain within the scope of the present invention.

[**0089**] FIG. **4** displays a block diagram of a computer **400** implemented in accordance with the teachings of the present invention. A central processing unit (CPU) **402** functions as the brain of the computer **400**. Internal memory **404** is shown. The internal memory **404** includes short-term memory **406** and long-term memory **408**. The short-term memory **406** may be Random Access Memory (RAM) or a memory cache used for staging information. The long-term memory **408** may be a Read Only Memory (ROM) or an alternative form of memory used for storing information. In one embodiment of the present invention, a short-term memory, such as RAM **406**, may be a display memory and used for storing a GUI for display on a monitor.

[**0090**] A storage memory **410**, such as a hard drive, is also shown. A pump control system **415**, such as the pump control chip **288** of FIG. **2** or pump control chip **300** of FIG. **3** is shown. In another embodiment, a pump control system **415** may be implemented using the other components of computer **400**, such as CPU **402**, storage memory **410**, internal memory **404**, communication pathway **412**, input interface **414**, output interface **416**, etc. For example, the logic implementing the functionality of the pump control system **415** may be implemented in RAM **406** or in ROM **408**. In yet another embodiment, input devices **418** and output devices **420** may be combined in a pump control system, such as pump control system **415**. In this configuration, the pump control system **415** may be implemented in a pump system and controlled by computer **400**. A communication pathway **412** is used to communicate information between short-term memory **406**, long-term memory **408**, storage memory **410**, input interface **414**, output interface **416**, CPU **402**, and the pump control system **415**.

[**0091**] Input devices, such as a joystick, a keyboard, a microphone, a communication connection, servo motor inputs, inlet control inputs, outlet control inputs, gradient control inputs, ADC inputs, a mouse, etc., are shown as **418**. The input devices **418** interface with the system through an input interface **414**. Output devices, such as a monitor, speakers, communication connections, servo motor outputs, inlet control outputs, outlet control outputs, gradient control outputs, ADC outputs, etc., are shown as **420**. The output devices **420** communicate with the computer **400** through an output interface **416**.

[**0092**] In one embodiment of the present invention, routines used to operate a pumping system, such as the pumping system **200** of FIG. **2**, may be stored in internal memory **404**, storage memory **410**, or in the pump control system **415**. The CPU **402** may operate under the control of these routines and control the pumping system **200** of FIG. **2** by communicating with input devices **418** and output devices **420**.

[**0093**] FIG. **5** displays a block diagram of an embodiment of a high-pressure gradient pumping system, such as a binary pumping system. Pumping system **500** includes two channels. The first channel includes a pumping unit **506** positioned in series (i.e., coupled to/in liquid communication) with a pumping unit **516**. The second channel includes a pumping unit **526** positioned in series (i.e., coupled to/in liquid communication) with a pumping unit **536**. The pumping unit **506** receives liquid through an inlet valve **504** and outputs liquid through an outlet valve **508**. The pumping unit **536** receives liquid through an inlet valve **538** and outputs liquid through an outlet valve **534**. Each pumping unit, such as **506**, **516**, **526**, and **536**, interfaces with a gear system **510**, **520**, **530**, and **540**, respectively. Further, each gear system **510**, **520**, **530**, and **540** interfaces with a motor/encoder unit **514**, **522**, **532**, and **544**, respectively. Lastly, each motor/encoder unit (i.e., **514**, **522**, **532**, and **544**) is in communication with a computer **524**. It should be appreciated that throughout the disclosure the gear system, such as gear system **510**, and the motor/encoder unit, such as motor/encoder unit **514**, may be considered a drive system used to drive the pumping unit, such as pumping unit **506**. It should also be appreciated that alternative forms of pumping units, such as syringe pumping units, etc., and alternative forms of drive systems may be implemented in each of the disclosed embodiments and may still remain within the scope of the present invention. For example, any conventional system (i.e., drive system) used to drive a pumping apparatus is within the scope of the present invention.

[**0094**] The first channel and the second channel are in parallel with each other and liquid flows from the pumping unit **516** and the pumping unit **526** into a mixing chamber **548**. The mixing chamber **548** is connected to a damper **550**. The damper **550** is connected to a mixer **552**, which in turn is connected to a purge valve **554**. Liquid flows from the purge valve **554** out as waste as shown by **556** or out to the remainder of the chromatography system as shown by **558**.

[0095] Each motor/encoder unit (i.e., **514**, **522**, **532**, and **544**) is connected to a computer **524**. As a result, each pumping unit (i.e., **506**, **516**, **526**, and **536**) may be controlled. In one embodiment of the present invention, metering of liquid and delivery of the liquid to the chromatography system are performed by individually controlling the operation of each pumping unit (i.e., **506**, **516**, **526**, and **536**) with the motor/encoder unit (i.e., **514**, **522**, **532**, and **544**) in conjunction with the computer **524**.

[0096] During operation, liquid flows from the liquid reservoirs as shown by **502** and **546** through an inlet valve **504** and an inlet valve **538**, respectively. Each motor/encoder unit (i.e., **514**, **522**, **532**, and **544**) interfaces with a gear system (i.e., **510**, **520**, **530**, and **540**) to individually operate each pumping unit (i.e., **506**, **516**, **526**, and **536**). For example, motor encoder unit **514** interfaces with gear system **510** to individually control pumping unit **506**. Motor/encoder unit **522** interfaces with gear system **520** to individually control pumping unit **516**. Motor/encoder unit **532** interfaces with gear system **530** to individually control pumping unit **526**. Lastly, motor/encoder unit **544** interfaces with gear system **540** to individually control pumping unit **536**.

[0097] In one embodiment, the motor/encoder unit **514** and the motor/encoder unit **522** are synchronized via computer **524** to enable a piston **512** in the pumping unit **506** and a piston **518** in the pumping unit **516** to operate at variable speeds relative to each other. In one embodiment, piston **512** may operate at some multiple of piston **518**. For example, piston **512** may operate at continuous multiple of 2×, 4×, 7×, etc. of piston **518**. In an alternative embodiment, piston **512** may operate at varying multiple of piston **518**. It should also be appreciated that the piston (i.e., **512**, **518**, **528**, and **542**) in each pumping unit (i.e., **506**, **516**, **526**, **536**) may operate at an equal speed, a speed that is a continuous multiple or varying multiple relative to each other. Operating a pumping unit relative to another pumping unit controls and/or manages the metering of liquid into and out of each pumping unit (i.e., **506**, **516**, **526**, **536**).

[0098] In one embodiment, during operation, liquid enters the pumping unit (i.e., **506**, **516**, **526**, **536**) in the bottom of a chamber and leaves the unit close to the top of a chamber. However, it should be appreciated that in alternate embodiments, liquid may enter and exit the chamber at different locations. In one embodiment, each chamber includes a piston, which has an outer diameter, which is smaller than the inner diameter of the chamber. As a result, liquid can fill the gap in between the outer diameter of the piston and the inner diameter of the chamber. In one embodiment, a piston has a stroke volume in the range of 20-100 ul as a function of the flow rate. A pump chip located in the computer **524** controls the flow rates in a range of nano-liters to milliliters. However, it should be appreciated that a wide range of stroke volumes and flow rates may be implemented and remain within the range of the present invention.

[0099] During operation, the pumping system **500** performs an initialization procedure to determine the upper dead center (UDC) and the lower dead center (LDC) for each piston (i.e., **512**, **518**, **528**, and **542**). In addition, during initialization, motor/encoder unit (i.e., **514**, **522**, **532**, **544**) are monitored to determine feedback movements, reference position signals are monitored, and assemblies are tested and monitored. Each piston (i.e., **512**, **518**, **528**, and **542**) moves upward slowly into the mechanical stop of the chamber and from there it moves back a defined path length. The computer **524** stores these piston positions in memory. After this initialization, the pumping system **500** starts operation with set parameters for each pumping unit (i.e., **506**, **516**, **526**, and **536**) in each channel.

[0100] Each inlet valve, such as **504** and **538**, is opened. The piston **512** in the pumping unit **506** and the piston **542** in the pumping unit **536** each perform an intake stroke to draw liquid into the pumping unit **506** and **536**, respectively. At the same time, pistons **518** and **528** in the pumping units **516** and **526** move upward delivering liquid to the mixing chamber **548**. After a controller-defined stroke length (depending on the flow rate), each motor/encoder unit (i.e., **514**, **522**, **532**, and **544**) is stopped and the inlet valves **504** and **538** are closed. The direction of each motor/encoder unit (i.e., **514**, **522**, **532**, and **544**) is reversed and pistons **512** and **542** move upward until they reach the stored upper limit (i.e., UDC), and at the same time, pistons **518** and **528** move downward.

[0101] The sequence repeats itself moving the pistons (i.e., **512**, **518**, **528**, and **542**) up and down between the two limits (i.e., UDC and LDC). During the upward movement of the pistons **512** and **542**, the liquid in pumping unit **506** and **536** is pressed through the outlet valves **508** and **534** into the pumping units **516** and **526**. The pistons **518** and **528** each draw in a portion of the volume displaced by the pistons **512** and **542** and the remaining volume is directly delivered to the system. During the drawing stroke of the pistons **512** and **542**, the pistons **518** and **528** deliver the drawn volume into the system.

[0102] FIG. **6** displays a block diagram of an embodiment of a low-pressure gradient pumping system, such as a quaternary pumping system. Pumping system **600** includes two pumping units (**616**, **632**) positioned in series. Liquids **602**, **604**, **606**, and **608** are processed through a vacuum chamber **610** and through a proportioning valve **612**. The proportioning valve **612** is in series with a pumping unit **616**, which is in series with a damper unit **630**, which is further in series with a pumping unit **632**. A purge valve **638** provides an outlet to the system as shown by **640** and to waste as shown by **642**. A gear system (i.e., **620**, **634**) and a motor/encoder unit (i.e., **624**, **636**) are connected to each pumping unit (i.e., **616**, **632**). Each motor/encoder unit (i.e., **624**, **636**) is coupled to a computer **628**, which controls each of the pumping units (i.e., **616**, **632**).

[0103] The pumping system **600** is based on a dual-pump configuration. Metering of liquid and delivery are regulated by operating each pumping unit (i.e., **616**, **632**) individually using the gear system (i.e., **620**, **634**), the motor/encoder unit (i.e., **624**, **636**), and the computer **628**. Degassing of liquids is performed in a vacuum chamber **610** and liquid compositions are generated by a high-speed proportioning valve **612**. In one embodiment, the pumping unit **616** includes an active inlet valve **614** and an outlet valve **618**. A damper unit **630** is connected between the two pumping units (i.e., **616** and **632**).

[0104] When turned on, the pumping system **600** runs through an initialization procedure to determine the upper dead center (UDC) of a piston **622** in the pumping unit **616**. The piston **622** moves slowly upward into the mechanical

stop of the chamber and from there it moves back a predetermined path length. The computer **628** stores the position of piston **622** in memory. The lower dead center (LDC) varies as a function of the flow rate, stroke length, etc. After initialization, the pumping system **600** starts operation with the parameters acquired during the initialization procedure. The active inlet valve **614** is opened and the down moving piston **622** draws liquid into the chamber. At the same time, the piston **626** is moving upward delivering liquid into the system. After a controller-defined stroke length (depending on the flow rate), the motor/encoder unit **624** is stopped and the active inlet valve **614** is closed. The motor/encoder unit **624** is reversed and moves the piston **622** up until it reaches the stored upper limit and at the same time, a second motor/encoder unit **638**, which controls the piston **626**, moves the piston **626** downward. The sequence then repeats itself with the two pistons (i.e., **622** and **626**) moving up and down between the two limits (i.e., reciprocating). During the up movement of the piston **622**, the liquid in the chamber is delivered through the outlet valve **618** into the damper unit **630**. The piston **626** draws in a portion of the volume displaced by the piston **622** from the damper unit **630** and the remaining amount of the volume is delivered to the system. During the intake stroke (i.e., drawing stroke) of the piston **622**, the piston **626** delivers the drawn volume to the system as shown in **640**. For liquid compositions that require percentages of liquids **602**, **604**, **606**, and **608**, the computer **628** controls and divides the length of the intake stroke into fractions and coordinates with the proportioning valve **612** to connect the specified liquid channel to the pumping units (i.e., **616**, **632**) to acquire the liquid in the proper percentages.

[**0105**] FIG. **7** displays a block diagram of a pumping system, such as a capillary pumping system. In FIG. **7**, liquid flows into a pumping system **700** through a conveyance or inlet tubes as shown by **702**, **704**, **706**, and **708**. The liquid flows through a vacuum chamber **710**. The liquid then flows through a solvent selection valve (SSV) **712** and a solvent selection valve (SSV) **732**. The SSV **712** is in series with a pumping unit **716**, which includes an inlet valve **714** and an outlet valve **718**. The pumping unit **716** is controlled by a gear system **720**, which is connected to a motor/encoder unit **724**. The pumping unit **716** is in series with a pumping unit **722**, which is controlled by a gear system **726** that is connected to a motor/encoder unit **728**.

[**0106**] The SSV **732** is connected to a pumping unit **734**, which is connected to a gear system **736**, which interfaces with a motor/encoder unit **738**. A pumping unit **740** is connected to a gear system **742**, which is connected to motor/encoder unit **744**. The pumping unit **722** and the pumping unit **740** are connected to a mixing chamber **746**. The mixing chamber **746** is in series with a damper **748**, which is in series with a mixer **750**. A variable nozzle **752** is positioned in series with the mixer **750**. The variable nozzle **752** controls the split ratio of the total flow between the flow of the flow sensor **756** and the flow to waste **754**. The flow sensor **756** is positioned on the output of the pumping system **700**.

[**0107**] FIG. **8** displays a block diagram of an embodiment of a high-pressure gradient pumping system, such as a preparative pumping system. To reduce the complexity of the high-pressure gradient pumping system **800**, a single channel is depicted in FIG. **8**. The liquid **802** is input into the pumping unit **808**, which is coupled to an inlet valve **806** and an outlet valve **810**. In addition, a liquid **804** is input into a pumping unit **820**, which is coupled to an inlet valve **818** and outlet valve **822**. The pumping unit **808** interfaces with a gear system **812**, which is controlled by a motor/encoder unit **814**.

[**0108**] In one embodiment of the high-pressure gradient pumping system **800**, the pumping unit **820** interfaces with a gear system **824**, which is controlled by a motor/encoder unit **826**. The piston **809** produces output shown as **828**. The pumping unit **820** produces output shown as **830**. The output **828** and the output **830** combine in a mixer **832**. The mixer **832** is in series with a purge valve **834**. The purge valve **834** is in series with a T-junction **838**. The T-junction **838** also receives liquid **840** from a second channel (not shown) of the pumping system **800**. It should be appreciated that FIG. **8** displays one channel of a pumping system **800**. A second channel of the pumping system **800**, which is not shown, replicates the first channel shown in FIG. **8**. The output of the second channel, liquid **840** is shown. A mixer **842** is in series with the T-junction **838** and mixes liquid **840** before the liquid **840** is output to the column as shown by **844**.

[**0109**] In another embodiment of the high-pressure gradient pumping system **800**, the high-pressure gradient pumping system **800** is implemented without the gear systems (i.e., **812**, **824**). In an alternative configuration, the pistons are coupled and driven by an encoder controlled motor.

[**0110**] FIG. **9**A displays a schematic diagram of a pumping system, such as a single-channel pumping system, where the pumping units are positioned in series. In one embodiment, the schematic diagram of pumping system **900** may represent a low-pressure gradient pumping system, where mixing occurs prior to the pumping units. In one embodiment, the switch **912** may represent a selection switch. In another embodiment, the switch **912** may represent a proportioning valve. It should be appreciated that the schematic diagram shown in FIG. **9**A may be used to represent an isocratic pump as shown in FIG. **2**, a single channel of a binary pump as shown in FIG. **5**, a quaternary pump as shown in FIG. **6**, a single channel of a capillary pump as shown in FIG. **7**, or a preparative pump as shown in FIG. **8**. It should also be appreciated that the methods presented in this application may be implemented on each of these pumping system configurations and, therefore, implementing any one of the methods presented in the instant application on any one of the pumping system configurations is within the scope of the present invention.

[**0111**] A variety of conventions have been employed in presenting the instant application. Throughout the instant application many figures include components that are outlined with dashed lines. Components outlined with dashed lines are used to display where the components may be positioned within the pumping system. However, each component may not be used in every configuration. For example, the pumping system **900** includes flow sensor **918**, flow sensor **932**, and flow sensor **942**. Each flow sensor (i.e., **918**, **932**, **942**) is outlined with dashed lines. Therefore, some of the methods presented below may utilize one of the flow sensors (i.e., **918**, **932**, **942**) or a combination of the flow sensors (i.e., **918**, **932**, **942**). For example, a method may utilize flow sensors **918**, **932**, or **942**. In the alternative, a method may utilize a combination of flow sensors **918** and

932, **932** and **942**, **918** and **942**, or **918**, **932**, and **942**. To identify which components are configured and/or implemented in the pumping system **900** during the discussion of a method operating on the pumping system **900**, referencing text explaining the method will identify the components that are configured and operating in the pumping system **900** during the performance of the method.

[**0112**] Throughout the course of the application, pumping units, such as **920** and **934**, are also outlined with dashed lines. The dashed lines presented around the pumping units (i.e., **920**, **934**) are provided to refer to the pumping units (i.e., **920**, **934**) with a single label (i.e., pumping unit). Although the methods presented in the instant application operate with at least two pumping units, variations and modifications of the method may be performed to work with a single pumping unit and are still within the scope of the present invention. Any discussion of methods that utilize pumping units will identify the pumping unit configuration.

[**0113**] FIG. **9**A displays two pumping units (i.e., **920**, **934**) in series. In one embodiment, the two pumping units (i.e., **920**, **934**), which are positioned in series comprise a channel. Further, as depicted in FIG. **9**A, an inlet valve **916** is in series with a flow sensor **918** which is in series with pumping unit **920**. Further, outlet valve **930** is in series with flow sensor **932**, which is in series with pumping unit **934**. Lastly, flow sensor **942** is in series with pumping unit **934**. As mentioned previously, flow sensors **918**, **932**, and **942** are represented in dashed lines, which depicts that different combinations of flow sensors **918**, **932** and **942** may be implemented when performing the methods presented in the instant applications. Therefore, a specific flow sensor (i.e., **918**, **932**, and **942**) will be discussed and described when the flow sensor is configured and operating during the performance of the method.

[**0114**] FIG. **9**A displays the schematic diagram of a pumping system **900**, which includes a variety of liquids (i.e., A, B, C, D) stored in a liquid reservoir **902**. Each liquid (i.e., A, B, C, D) is conveyed through a conveyance **904**, **906**, **908**, and **910** to a switch **912**. When the switch **912** is implemented as a proportioning valve, the liquids (i.e., A, B, C, D) are mixed. The liquids (i.e., A, B, C, D) are then drawn through an inlet valve **916** into a pumping unit **920**. The pumping unit **920** includes a chamber **922** and a piston **924**, which performs a reciprocating motion (i.e., performs a piston stroke which consist of an intake stroke and a delivery stroke). An outlet valve **930** is in series with the pumping unit **920**. A flow sensor **932** is in series with the outlet valve **930**. A pumping unit **934** is in series with the flow sensor **932**, which is in series with the outlet valve **930**. The pumping unit **934** includes a chamber **936** and a piston **938**. Throughout the discussion of the figures in the present invention, inlet valves and outlet valves will be described and discussed. It should be appreciated that the inlet valves, such as inlet valve **916** and the outlet valves, such as outlet valve **930**, may be implemented as active valves or passive valves. In addition, the flow sensors, such as flow sensor **918**, may be positioned before the inlet valve **916** or after the inlet valve **916** and the flow sensor **932** may be positioned before the outlet valve **930** or after the outlet valve **930**. A wide variety of flow sensors may be implemented in accordance with the teachings of the present invention. One specific flow sensor that may be implemented in the present invention is flow sensor model SLG **1430** implemented by Sensirion, Switzerland.

[**0115**] A motor/encoder system (i.e., drive system) **926** and a motor/encoder system (i.e., drive system) **940** each include the gears (i.e., gear system), the motor, and the encoders (i.e., motor/encoder system) required to individually operate the pumping unit **920** and the pumping unit **934**, respectively. A computer **928** is coupled to both the motor/encoder system **926** and the motor/encoder system **940**.

[**0116**] During initialization, procedures are performed to identify the upper dead center (UDC) and lower dead center (LDC) of the piston **924** and piston **938** using the motor/encoder system (i.e., **926**, **940**). Additional activities, such as opening and closing the inlet valve **916** and the outlet valve **930**, may also be performed during initialization.

[**0117**] During operation, the inlet valve **916** is opened. An intake stroke of the piston **924** draws liquid (i.e., A, B, C, D) through the switch **912** and fills the chamber **922**. In one embodiment, liquids **922**A, **922**B, **922**C, and **922**D are drawn into the chamber **922** and correspond to the liquid A, B, C and D stored in liquid reservoir **902**. Various percentages of liquids (i.e., A, B, C, D) are mixed together when the switch **912** is implemented as a proportioning valve. On the delivery stroke of the piston **924**, liquid (i.e., **922**A, **922**B, **922**C, **922**D) is compressed and forced out of the chamber **922** through the outlet valve **930**. The motor/encoder system **926** in conjunction with computer **928** are used to adjust the intake and delivery stroke of the piston **924** to adjust the metering (i.e., intake and expulsion) of liquid (i.e., **922**A, **922**B, **922**C, **922**D) from the chamber **922**. In a similar manner, the motor/encoder system **940** in conjunction with computer **928** are used to adjust the intake and delivery stroke of the piston **938** to meter (i.e., adjust the intake and expulsion of liquid) from the chamber **936**.

[**0118**] Metering is implemented using a number of alternative mechanisms. In one embodiment, metering is performed by individually controlling the pumping unit **920** with the motor/encoder system **926** and computer **928**. In another embodiment, metering is accomplished by individually controlling the pumping unit **934** with the motor/encoder system **940** and the computer **928**. In another embodiment, metering is performed by integrating and controlling the operation of the pumping units **920** and **934** with the motor/encoder systems **926** and **940** and computer **928**. Lastly, metering may involve an integrated system operation controlling the flow rate of liquid throughout the entire pumping system **900** (i.e., single-channel pump). Metering in this context may include using various components in addition to the pumping unit **920** or the pumping unit **934**. Therefore, metering using an integrated system may include using the inlet valve **916**, the flow sensor **918**, the pumping unit **920**, the outlet valve **930**, the flow sensor **932**, the pumping unit **934**, the flow sensor **942**, and the output sensor **944**, selectively or in combination to meter the flow of liquid through the pumping system **900**.

[**0119**] FIG. **9**B displays the schematic diagram of a pumping system, such as a single channel of a pumping system with pumping units configured in parallel. FIG. **9**B displays two pumping units (i.e., **958**, **978**) in parallel. In one embodiment, the two pumping units (i.e., **958**, **978**) are positioned in parallel and are implemented in a channel of

pumping system **950**. Inlet valve **954**, flow sensor **956**, pumping unit **958**, outlet valve **966**, and flow sensor **968** are positioned in series. Inlet valve **974**, flow sensor **976**, pumping unit **978**, outlet valve **986**, and flow sensor **988** are positioned in series. Flow sensor **994** is positioned in parallel with flow sensor **968**. In addition, flow sensor **994** is positioned in parallel with flow sensor **988**.

[**0120**] A liquid is conveyed from reservoir **952** through an inlet valve **954** and through a flow sensor **956** to the pumping unit **958**. The pumping unit **958** is in series with the flow sensor **956**. It should be appreciate that the flow sensor **956** may be configured before the inlet valve **954** or after the inlet valve **954**. Liquid is drawn from the reservoir **952** into the pumping unit **958** during an intake stroke. The pumping unit **958** includes a chamber **960** and a piston **962**, which performs a reciprocating motion (i.e., performs a piston motion which consists of a delivery stroke and an intake stroke). An outlet valve **966** is positioned in series with the pumping unit **958**. A flow sensor **968** is in series with the outlet valve **966**. It should be appreciated that the flow sensor **968** may be configured before the outlet valve **966** or after the outlet valve **966**. An output **970** is also shown.

[**0121**] Liquid is conveyed from the reservoir **952** through an inlet valve **974** and through a flow sensor **976** to the pumping unit **978**, which is in series with the flow sensor **976**. It should be appreciate that the flow sensor **976** may be configured before the inlet valve **974** or after the inlet valve **974**. Liquid is drawn from the reservoir **952** into the pumping unit **978** during an intake stroke. The pumping unit **978** includes a chamber **980** and a piston **982**, which perform a reciprocating motion (i.e., performs a piston motion which consists of a delivery stroke and an intake stroke). An outlet valve **986** is positioned in series with the pumping unit **978**. A flow sensor **988** is in series with the outlet valve **986**. It should be appreciated that the flow sensor **988** may be configured before the outlet valve **986** or after the outlet valve **986**. An output **992** is also shown. Both output **970** and output **992** connect at a channel output **996**. A flow sensor **994** is positioned in the channel output **996**.

[**0122**] A motor/encoder system **964** is connected to the pumping unit **958**. The motor/encoder system **964** is controlled by a computer **990**. A motor/encoder system **984** is connected to a pumping unit **978**. The motor/encoder system **984** is controlled by the computer **990**.

[**0123**] During initialization, procedures are performed to identify the upper dead center (UDC) and lower dead center (LDC) of the piston **962** and piston **982** using the motor/encoder system (i.e., **964**, **984**). Additional activities, such as opening and closing the inlet valve **954** and **974**, and the outlet valve **966** and **986** may also be performed during initialization.

[**0124**] During operation, an inlet valve, such as **954** and/or **974**, is opened. An intake stroke of a piston, such as **962** and/or **982**, draws liquid from reservoir **952**. The liquid is drawn through an inlet valve, such as **954** and/or **974**, and through a flow sensor, such as **956** and/or **976**, respectively. The liquid fills a chamber, such as **960** and/or **980**, on the intake stroke. The piston **962** and/or **982** performs a delivery stroke and liquid stored in chambers **960** and **980** is compressed and forced out of the chambers **960** and **980** and through outlet valves **966** and **986**, respectively. The liquid flows through flow sensors **968** and **988** to outputs **970** and **992**. Outputs **970** and **992** combine at a channel output **996**. The liquid flows through a flow sensor **994** positioned on the channel output **996**. The motor/encoder system **964** and **984** in conjunction with computer **990** are used to adjust the intake and delivery stroke of the pistons **962** and **982**, respectively, to adjust the metering (i.e., intake and delivery) of liquid from the chambers **960** and **980**.

[**0125**] FIG. **10** displays a schematic diagram of a pumping system, such as a dual-channel pumping system. In one embodiment, pumping system **1000** may represent a high-pressure gradient pumping system, such as the pumping systems represented in FIG. **5** and FIG. **7**. In a first channel, inlet valve **1004**, flow sensor **1005**, pumping unit **1006**, outlet valve **1016**, flow sensor **1018**, pumping unit **1020**, and flow sensor **1030** are positioned in series. In a second channel, inlet valve **1042**, flow sensor **1043**, pumping unit **1044**, outlet valve **1052**, flow sensor **1054**, pumping unit **1056**, and flow sensor **1038** are positioned in series. The first channel and the second channel are parallel to each other. The first channel and the second channel combined are in series with flow sensor **1032**. It should be appreciated that although FIG. **10** displays a dual-channel pumping system with pumping units configured in series, the methods presented in the instant application may also be implemented in a dual-channel pumping system where the pumping units are positioned in parallel.

[**0126**] Pumping system **1000** includes a liquid stored in a liquid reservoir **1002**. The liquid stored in the liquid reservoir **1002** is drawn through a flow sensor **1005** and through an inlet valve **1004** into a pumping unit **1006**. The pumping unit **1006** includes a chamber **1008** and a piston **1010**, which reciprocate upward and downward within the chamber **1008**. On the intake stroke of the piston **1010**, liquid fills the chamber **1008** and on the delivery stroke of the piston **1010**, liquid is compressed and forced out of the chamber **1008**. A motor/encoder system **1012** in conjunction with a computer **1014** are used to meter the intake and expulsion (i.e., flow) of liquid into and out of the chamber **1008** by adjusting (i.e., position, such as stroke length and/or timing) the upward and intake stroke of the piston **1010**

[**0127**] An outlet valve **1016** is positioned in series with the pumping unit **1006**. A flow sensor **1018** is positioned in series with the outlet valve **1016** (note: can be located before or after the outlet valve **1016**) and detects the flow of liquid between the pumping unit **1006** and the pumping unit **1020**. A piston **1024** operates within the chamber **1022**. Liquid flows from the pumping unit **1006** to the pumping unit **1020**. Liquid fills the chamber **1022** and on the delivery stroke of the piston **1024**, liquid is forced out of the chamber **1022**. In addition, in an alternate embodiment, liquid from chamber **1008** flows through chamber **1022** directly to channel output **1028** if piston **1024** is stationary or moving upwards. It should be appreciated that a variety of embodiments may be implemented and still remain within the scope of the present invention. A motor/encoder system **1026** in conjunction with the computer **1014** are used to meter (i.e., adjust the upward and intake stroke) the flow of liquid from the piston **1024**.

[**0128**] The pumping system **1000** includes a liquid reservoir **1040**. Liquid is drawn through flow sensor **1043** and through inlet valve **1042**. The liquid is then drawn into a pumping unit **1044**. The pumping unit **1044** includes a chamber **1046** and a piston **1048**, which reciprocates upward

and downward within the chamber **1046**. On the intake stroke of the piston **1048**, liquid fills the chamber **1046** and on the delivery stroke of the piston **1048**, liquid is compressed and forced out of the chamber **1046**. A motor/encoder system **1050** in conjunction with a computer **1014** are used to meter the flow of liquid into and out of the chamber **1046** by adjusting (i.e., position, such as stroke length and/or timing) the upward and intake stroke of the piston **1048** to adjust the intake and expulsion of liquid from the chamber **1046**.

[**0129**] An outlet valve **1052** is positioned in series with the pumping unit **1044**. A flow sensor **1054** is positioned in series with the outlet valve **1052** and detects the flow of liquid between the pumping unit **1044** and the pumping unit **1056**, which is in series with the pumping unit **1044**. A piston **1060** operates within the chamber **1058**. Liquid flows from the pumping unit **1044** to the pumping unit **1056**. Liquid fills the chamber **1058** on an intake stroke of piston **1060** and on the delivery stroke of the piston **1060**, liquid is compressed and forced out of the chamber **1058**. In addition, in an alternate embodiment, liquid from chamber **1046** flows through chamber **1058** directly to channel output **1036** if piston **1060** is stationary or moving upwards. As previously stated, it should be appreciated that a variety of embodiments may be implemented and still remain within the scope of the present invention. A motor/encoder system **1062** in conjunction with the computer **1014** are used to meter (i.e., adjust the intake and delivery stroke) the flow of liquid from the chamber **1058** and to adjust the intake and expulsion of liquid from the chamber **1058**.

[**0130**] In one embodiment, pumping unit **1006** and pumping unit **1020** combine to form a first channel, which outputs liquid to a first channel output **1028**. In another embodiment, pumping unit **1044** and pumping unit **1056** combine to form a second channel, which outputs liquid to a second channel output **1036**. Both the first channel output **1028** and the second channel output **1036** are coupled to a pumping system output shown as **1034**. Therefore, the combined liquid conveyed on the first channel output **1028** and the liquid conveyed on the second channel output **1036** is conveyed on the pumping system output **1034**.

[**0131**] In one embodiment, a flow sensor **1030** is positioned on the first channel output **1028** and detects the flow of liquid conveyed on the first channel output **1028**. In another embodiment, a flow sensor **1038** is positioned on the second channel output **1036** and detects the flow of liquid conveyed on the second channel output **1036**. In another embodiment, a flow sensor **1032** is positioned on the pumping system output **1034** and detects the flow of liquid conveyed on the pumping system output **1034**.

[**0132**] FIG. **11**A displays a flow diagram depicting a method of configuring sensors in a pumping system. FIGS. **9**A, **9**B, and **10** will be discussed in conjunction with FIG. **11**A. At step **1100**, a pumping system, such as the pumping system represented by the schematic diagrams depicted in FIGS. **9**A, **9**B, and **10**, are configured with flow sensors. Configuring may include manufacturing the pumping system with a specific configuration of flow sensors or implementing (i.e., operating) a specific configuration of flow sensors in the pumping system during operation of the pumping system. Implementing a specific configuration of flow sensors may include real-time operation of flow sensors connected to the pumping system, non-real time implementation of flow sensors between testing, etc.

[**0133**] In one embodiment, selected flow sensors are implemented in the pumping system to individually detect the flow of liquid in the pumping system. In another embodiment, flow sensors are implemented in the pumping system and simultaneously operate to detect and compare the flow of liquid throughout the pumping system. For example, referring to FIG. **9**A, flow sensors **918**, **932**, and **942** may each individually be implemented within the pumping system and work individually to detect liquid flow within the pumping system. In another embodiment, flow sensors **918**, **932**, and **942** may all be implemented within the pumping system and work collaboratively to detect and determine the flow of liquid throughout the pumping system. Lastly, any combination of flow sensors may be implemented and operate collectively within the pumping system.

[**0134**] Referring to FIG. **9**B, flow sensors **956**, **968**, **976**, **988**, and **994** may each individually be implemented within the pumping system and work individually to detect liquid flow within the pumping system. In another embodiment, flow sensors **956**, **968**, **976**, **988**, and **994** may all be implemented within the pumping system and work collaboratively to detect and determine the flow of liquid throughout the pumping system. Lastly, any combination of flow sensors **956**, **968**, **976**, **988**, and **994** may be implemented and operate collectively within the pumping system.

[**0135**] A similar methodology may be implemented using FIG. **10** as a reference. Flow sensors **1005**, **1018**, **1030**, **1032**, **1038**, **1043**, and **1054** may each be implemented individually or collectively in the pumping system **1000**. Further, any combination or permutation of the flow sensors **1005**, **1018**, **1030**, **1032**, **1038**, **1043**, and **1054** may be implemented in the pumping system **1000**.

[**0136**] Once the flow sensors are configured, the pumping system performs normal operations as shown by **1102**. At step **1104**, leaks may be determined by using the flow sensors. A variety of techniques may be used to determine leaks using the flow sensors. For example, 1) a change in the flow rate recorded by a flow sensor over time may suggest a leak in a pumping system; 2) a comparison between the flow rate metered by the motor/encoder system and the flow rate measured by a flow sensor may identify a leak; 3) a comparison in flow rates measured by different flow sensors within the channel or between channels may suggest a leak in a pumping system; and 4) a comparison of flow rates metered by different pumping units within the channel or between the channels may suggest a leak in a pumping system. While specific examples of determining a leak with a flow sensor are provided, numerous examples for determining leaks with a flow sensor are presented in the instant application and are within the scope of the present invention. At step **1106**, once a leak is determined, compensation is made for the leaks in the pumping system. For example, each pumping unit may be controlled to compensate for the leaks by varying the metering of liquid flowing through each pumping unit.

[**0137**] FIG. **11**B displays a flow diagram depicting a method of reconfiguring sensors in a pumping system. FIGS. **9**A, **9**B, and **10** will be discussed in conjunction with FIG. **11**B. At step **1120**, a pumping system, such as the pumping system represented by the schematic diagram depicted in

FIGS. **9**A, **9**B, and **10**, is configured with flow sensors. Configuring may include manufacturing the pumping system with a specific configuration of flow sensors or implementing/operating (i.e., turning on and off) a specific configuration of flow sensors in the pumping system during operation of the pumping system.

[**0138**] In one embodiment, selected flow sensors are implemented in the pumping system individually to detect the flow of liquid in the pumping system. In another embodiment, flow sensors are implemented in the pumping system and simultaneously operate to detect and compare the flow of liquid throughout a pumping system. For example, referring to FIG. **9**A, flow sensors **918**, **932**, and **942** may each be individually implemented within the pumping system and work individually to detect flow within the pumping system. In another embodiment, flow sensors **918**, **932**, and **942** may all be implemented within the pumping system and/or work collaboratively to detect and determine the flow of liquid throughout the pumping system. Referring to FIG. **9**B, flow sensors **956**, **968**, **976**, **988**, and **994** may each individually be implemented within the pumping system and work individually to detect liquid flow within the pumping system. In another embodiment, flow sensors **956**, **968**, **976**, **988**, and **994** may all be implemented within the pumping system and work collaboratively to detect and determine the flow of liquid throughout the pumping system. Lastly, any combination of flow sensors **956**, **968**, **976**, **988**, and **994** may be implemented and operate collectively within the pumping system.

[**0139**] A similar methodology may be implemented using FIG. **10** as a reference. Flow sensors **1005**, **1018**, **1030**, **1032**, **1038**, **1043** and **1054** may each be implemented individually or collectively in the pumping system **1000**. Further, any combination or permutation of the flow sensors **1005**, **1018**, **1030**, **1032**, **1038**, **1043**, and **1054** may be implemented in the pumping system **1000**. It should also be appreciated that any combination of the foregoing methods or configurations may be implemented and still remain within the scope of the present invention.

[**0140**] Once the flow sensors are configured into a first configuration as stated at **1120**, the pumping system performs normal operations as shown by **1122**. At step **1124**, leaks may be determined by using the flow sensors. A variety of techniques may be used to determine leaks using the flow sensors. For example, a change in the flow rate, such as a decrease in the flow rate indicated by the flow sensor over time, may suggest a leak. While a specific example of determining a leak with a flow sensor is provided in this example, numerous examples for determining leaks with a flow sensor are presented in the instant application and are within the scope of the present invention.

[**0141**] At step **1126**, techniques, such as metering, are used to compensate for the leaks determined while operating the pumping systems. At step **1128**, the flow sensors are reconfigured into a second configuration. In one embodiment, reconfiguring the flow sensors may occur in real time during testing operations. In another embodiment, reconfiguring the flow sensors may occur in non-real time. In one embodiment, reconfiguration includes implementing a different configuration of flow sensors in the pumping system. At step **1130**, leaks are determined using the new configuration (i.e., reconfiguration) of flow sensors. For example, 1) a change in the flow rate recorded by a flow sensor over time may suggest a leak in a pumping system; 2) a comparison between the flow rate metered by the motor/encoder system and the flow rate measured by a flow sensor may identify a leak; 3) a comparison in flow rates measured by different flow sensors within the channel or between channels may identify a leak; and 4) a comparison of flow rates metered by different pumping units within the channel or between the channels may identify a leak. Further, each of these methods of determining leaks when the flow sensors are configured in the second configuration (i.e., **1128**) may be compared against the methods of determining leaks when the flow sensors are configured in the first configuration (i.e., **1120**). The comparison may then be used to determine leaks. At **1132**, compensation is made for the leaks in the pumping system. For example, each pumping unit may be controlled to compensate for the leaks by varying the metering of liquid from each pumping unit.

[**0142**] A number of alternative embodiments may be implemented using FIG. **11**B. For example, after operating the pumping system as stated at **1122**, the step of reconfiguring the sensors as stated at step **1128** may be performed. Once the step of re-configuring the flow sensors as stated at **1128** is performed, then the step of determining leaks is performed as stated at step **1130**, and the step of compensating for the leaks may be performed as stated at step **1132**. In alternate embodiments, the step of reconfiguring the sensors **1128** may be performed after the step of operating the pumping system as stated at **1122** or after the step of determining leaks as stated at **1124**. Once the step of reconfiguring the sensors as stated at **1128** is performed, then the step of determining leaks is performed as stated at step **1130**, and the step of compensating for the leaks may be performed as stated at step **1132**. It should be appreciated that a variety of permutations and combinations of the various methods depicted by the flow diagram shown in FIG. **11**B may be performed without departing from the spirit or scope of the invention.

[**0143**] FIG. **11**C displays a flow diagram depicting a method of calibrating flow sensors. FIGS. **9**A, **9**B, and **10** will be discussed in conjunction with FIG. **11**C. At **1130** of FIG. **11**C, the operation of a pumping system is characterized to determine leaks or the tightness of each pumping unit. In one embodiment, the pumping unit is characterized by determining the tightness of the pumping unit. To determine the tightness of the pumping unit, each pumping unit 1) is blocked (i.e., the inlet valve and the outlet valve surrounding the pumping unit is closed, the pumping unit is manually blocked online or offline, etc.); 2) the pressure in the pumping unit (i.e., chamber) is increased; and then 3) the pressure in the pumping unit (i.e., chamber) is monitored for a decrease in pressure. For example, using FIG. **9**A as an example, the piston **924** performs an intake stroke to draw liquid into the chamber **922**. The inlet valve **916** and the outlet valve **930** are then closed. The piston **924** moves through part of a delivery stroke to pressurize the chamber **922**. Lastly, the chamber **922** is monitored for a decrease in pressure. If there is a decrease in pressure, this signals a leak in the pumping unit. If there is no pressure decrease, then there are no leaks (i.e., the pumping unit is tight). This process may be performed for each pumping unit in the pumping systems shown in FIGS. **9**A, **9**B, and **10** to determine the tightness of each pumping unit.

[0144] At step **1132** of FIG. **11**C, the liquid is then metered out of the pumping unit. Metering the liquid involves individually controlling and recording the movement of an encoder found in the motor/encoder system to determine the exact amount of liquid that is being delivered out of a chamber in a pumping unit. For example, metering the liquid may involve recording the movement of an encoder found in the motor/encoder system **926** to determine the amount of liquid output from the chamber **922**. In an alternate embodiment, the liquid may be metered out of the chamber **922** at different flow rates and then measured by a flow sensor that we are attempting to calibrate.

[0145] Lastly, at step **1134**, a calibration factor is determined. To determine the calibration factor, a graph, such as the graph shown in FIG. **11**D, may be used. The graph shown in FIG. **11**D includes a voltage on the y-axis and the flow rate on the x-axis. A curve representing a calibration curve for a know solvent **1136** when the known solvent is used with a flow sensor is presented. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is shown. An unknown solvent is then processed through the flow sensor with a known flow rate. The voltage of the unknown solvent (i.e., solvent in the chamber) **1140** at a known flow rate **1142** is shown. The calibration factor depicted by **1144** is then defined by a relation between the voltage of the unknown solvent **1140** and the voltage of the known solvent **1138**. In one embodiment, the calibration factor **1144** is equivalent to the voltage of the unknown solvent **1140** divided by the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[0146] An alternate method of calibrating a flow sensor is presented using the flowchart depicted in FIG. **11**C, the graph presented in FIG. **11**D, and the pumping unit depicted in FIG. **9**A. In the alternate embodiment, a method of calibrating solvents in a low-pressure gradient pump is presented. At **1130** of FIG. **11**C, the operation of a pumping system is characterized to determine leaks or the tightness of each pumping unit. For example, using FIG. **9**A as an example, the piston **924** performs an intake stroke to draw liquid into the chamber **922**. In the alternate embodiment of the present invention, the valve **912** is switched to allow liquids conveyed on **904**, **906**, **908**, and **910** to be accessed from the reservoir **902** and transported on conveyance **914**. The liquid is then stacked in chamber **922** as shown by liquid **922**A, liquid **922**B, liquid **922**C, and liquid **922**D. The inlet valve **916** and the outlet valve **930** are then closed. The piston **924** moves through part of a delivery stroke to pressurize the chamber **922**. Lastly, the chamber **922** is monitored for a decrease in pressure. In one embodiment, the decrease in pressure may be measured using a pressure sensor (not shown) positioned to measure the pressure in chamber **922**. It should be appreciated that a pressure sensor may be deployed in each chamber of the pumping units presented in FIGS. **9**A, **9**B, and **10**. The pressure for the chamber in each of the pumping units may then be measured by the pressure sensor using methods presented in the instant application. Lastly, additional methods of determining a decrease in the pressure of the chamber may be implemented and are within the scope of the present invention. If there is a decrease in pressure, this signals a leak in the pumping unit. If there is no pressure decrease, then there are no leaks (i.e., the pumping unit is tight). This process may be performed for each pumping unit in the pumping systems shown in FIGS. **9**A, **9**B, and **10** to determine the tightness of each pumping unit.

[0147] At step **1132** of FIG. **11**C, the liquid is then metered out of the pumping unit. Metering the liquid involves individually controlling and recording the movement of an encoder found in the motor/encoder system to determine the exact amount of liquid that is being delivered out of a chamber in a pumping unit. For example, metering the liquid may involve recording the movement of an encoder found in the motor/encoder system **926** to determine the amount of liquid output from the chamber **922**. In an alternate embodiment, the liquid may be metered out of the chamber **922** at different flow rates and then measured by a flow sensor that we are attempting to calibrate.

[0148] In one embodiment, metering is performed to deliver each liquid and then calibration is performed relative to each liquid. For example, liquid **922**A, liquid **922**B, liquid **922**C, and liquid **922**D are each metered out of the chamber and used to calibrate flow sensor **918** and/or flow sensor **932**. The flow sensors are calibrated after each liquid is metered out of the chamber. For example, at step **1134**, a calibration factor is determined. To determine the calibration factor, a graph, such as the graph shown in FIG. **11**D, may be used. The graph shown in FIG. **11**D includes a voltage on the y-axis and the flow rate on the x-axis. A curve representing a calibration curve for a know solvent **1136** when the known solvent is used with a flow sensor is presented. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid **922**A, liquid **922**B, liquid **922**C, and liquid **922**D, is then processed through the flow sensor at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[0149] In the following, the method of calibrating a flow sensor depicted in FIG. **11**B will be described with respect to several configurations in FIG. **9**A. For example, a method of calibrating flow sensor **918** is presented. A method of calibrating flow sensor **932** is presented, and a method of calibrating flow sensor **942** is presented. In the method of calibrating flow sensor **918**, a test as described above is performed to determine the tightness of the pumping unit **920**. The inlet valve **916** is then opened and the outlet valve **930** is closed, and the liquid stored in the chamber **922** is metered out of the chamber **922** and through the flow sensor **918**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid **922**A, liquid **922**B, liquid **922**C, and liquid **922**D, is then processed through flow sensor **918** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[0150] To calibrate flow sensor **932**, a test as described above is performed to determine the tightness of the pumping unit **920**. The outlet valve **930** is then opened, the inlet valve **916** closed, and the liquid (i.e., unknown solvent) stored in the chamber **922** is metered out of the chamber **922**

and through the flow sensor **932**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid **922**A, liquid **922**B, liquid **922**C, and liquid **922**D, is then processed through flow sensor **932** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[**0151**] To calibrate flow sensor **942**, a test as described above is performed to determine the tightness of the pumping unit **920** and the pumping unit **934**. A variety of testing methods may be used to calibrate a flow sensor placed on an output of a low-pressure gradient pumping system. In one embodiment, the pumping unit **920** is used to calibrate the flow sensor **942**. In a second embodiment, the pumping unit **934** is used to calibrate the flow sensor **942**. In a third embodiment, a combination of the pumping unit **920** and the pumping unit **934** are used to test the flow sensor **942**.

[**0152**] In one embodiment, a test is made to determine the tightness of the pumping unit **920** and pumping unit **934**. Liquid stored in the pumping unit **920** is metered out of the chamber **922**, through the flow sensor **932**, through the chamber **936**, and through the flow sensor **942**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid **922**A, liquid **922**B, liquid **922**C, and liquid **922**D, is then processed through flow sensor **942** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[**0153**] In a second embodiment, a test is made to determine the tightness of the pumping unit **934**. The liquid stored in the pumping unit **934** is metered out of the chamber **936** and through the flow sensor **942**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid **922**A, liquid **922**B, liquid **922**C, and liquid **922**D, is then processed through flow sensor **942** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[**0154**] In a third embodiment, a test is made to determine the tightness of the pumping unit **920** and the pumping unit **934**. The liquid stored in the pumping unit **920** is metered out of the chamber **922** and through the flow sensor **932**, through the chamber **936**, and through the flow sensor **942**. The liquid stored in the pumping unit **934** is metered out of the chamber **936** and through the flow sensor **942**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid **922**A, liquid **922**B, liquid **922**C, and liquid **922**D, is then processed through flow sensor **942** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[**0155**] FIG. **9**B will be discussed in conjunction with FIG. **11**C. At **1130** of FIG. **11**C, the operation of a pumping system is characterized to determine leaks or the tightness of each pumping unit. For example, using FIG. **9**B as an example, the piston **962** and/or **982** performs an intake stroke to draw liquid into the chamber **960** and/or **980**. The inlet valve **954** and/or **974** and the outlet valve **966** and/or **986** are then closed. The piston **962** and/or **982** may each move through part of a delivery stroke to pressurize the chamber **960** and/or **980**. Lastly, the chamber **960** and/or **980** is monitored for a decrease in pressure. If there is a decrease in pressure, this signals a leak in the pumping unit (i.e., **958**, **978**). If there is no pressure decrease, then there are no leaks (i.e., the pumping unit is tight). This process may be performed for each pumping unit (i.e., **958**, **978**) in the pumping system **950** shown in FIG. **9**B to determine the tightness of each pumping unit (i.e., **958**, **978**).

[**0156**] At step **1132** of FIG. **11**C, the liquid is then metered out of the pumping unit. Metering the liquid involves individually controlling and recording the movement of an encoder found in the motor/encoder system to determine the exact amount of liquid that is being delivered out of a chamber in a pumping unit. For example, metering the liquid may involve recording movement of an encoder found in the motor/encoder system **964** and/or **984** to determine the amount of liquid output from the chamber **960** and/or **980**. In an alternate embodiment, the liquid may be metered out of the chamber **960** and/or **980** at different flow rates and then measured by a flow sensor that we are attempting to calibrate.

[**0157**] Lastly, at step **1134**, a calibration factor is determined. To determine the calibration factor, a graph, such as the graph shown in FIG. **11**D, may be used. The graph shown in FIG. **11**D includes a voltage on the y-axis and the flow rate on the x-axis. A curve representing a calibration curve for a know solvent **1136** when the known solvent **1136** is used with a flow sensor is presented. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in reservoir **952**, is then processed through a flow sensor (i.e., **956**, **968**, **976**, **988**, **994**) at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[**0158**] The method of calibrating a sensor depicted in FIG. **11**C will be described with respect to several configurations in FIG. **9**B. For example, a method of calibrating flow sensor **956** is presented, a method of calibrating flow sensor **968** is presented, a method of calibrating flow sensor **976** is presented, a method of calibrating flow sensor **988** is presented, and a method of calibrating flow sensor **994** is presented. In the method of calibrating flow sensor **956**, the pumping system **950** is characterized to determine leaks in the pumping system **950**. The inlet valve **954** is then opened and the outlet valve **966** is closed, and the liquid stored in the chamber **960** is metered out of the chamber **960** and through the flow sensor **956**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in reservoir **952**, is then processed through a flow sensor **956**

at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[**0159**] To calibrate flow sensor **968**, the pumping system **950** is characterized to determine the tightness of the pumping units **958** and **978**. The outlet valve **966** is then opened, inlet valve **954** is closed, and the liquid stored in the chamber **960** is metered out of the chamber **960** and through the flow sensor **968**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in reservoir **952**, is then processed through a flow sensor **968** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates. In one embodiment of the present invention, the foregoing methods may also be used to calibrate flow sensors **976** and **988**.

[**0160**] A variety of testing methods may be used to calibrate a flow sensor placed on an output, such as the flow sensor **994**, which is positioned on the output of pumping system **950**. In one embodiment, the pumping unit **958** is used to calibrate the flow sensor **994**. In a second embodiment, the pumping unit **978** is used to calibrate the flow sensor **994**. In a third embodiment, a combination of the pumping unit **958** and the pumping unit **978** are used to calibrate flow sensor **994**.

[**0161**] To calibrate flow sensor **994**, the pumping system **950** is characterized to determine the tightness of the pumping units **958** and the pumping unit **978**. Liquid stored in the pumping unit **958** is metered out of the chamber **960**, through the flow sensor **968**, and through the flow sensor **994**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in reservoir **952**, is then processed through a flow sensor **994** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates. It should be appreciated that flow sensors **968** and **994** may both be calibrated using the foregoing methods and then compared to provide a more accurate calibration factor **1144** for each flow sensor (i.e., **968**, **994**).

[**0162**] In a second embodiment, the pumping system **950** is characterized to determine the tightness of the pumping units **958** and the pumping unit **978**. Liquid stored in the pumping unit **978** is metered out of the chamber **980** through the flow sensor **988** and through the flow sensor **994**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in reservoir **952**, is then processed through a flow sensor **994** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates. It should be appreciated that flow sensors **988** and **994** may both be calibrated using the foregoing methods and then compared to provide a more accurate calibration factor **1144** for each flow sensor (i.e., **988**, **994**).

[**0163**] In a third embodiment, the pumping system **950** is characterized to determine the tightness of the pumping unit **958** and the pumping unit **978**. The liquid stored in the pumping unit **958** is metered out of the chamber **960** through the flow sensor **968** and through the flow sensor **994**. The liquid stored in the pumping unit **978** is metered out of the chamber **980** through the flow sensor **988** and through the flow sensor **994**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in reservoir **952**, is then processed through a flow sensor **994** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[**0164**] The method of calibrating a flow sensor depicted in FIG. **11**C will be described with respect to several configurations in FIG. **10**. The calibration method depicted in FIG. **11**C is applied to each configuration to calibrate one of the flow sensors. In the following discussion, methods are presented for calibrating flow sensors **1005**, **1018**, **1030**, **1032**, **1038**, **1043**, and **1054**.

[**0165**] In the method of calibrating flow sensor **1005**, the pumping system **1000** is characterized to determine the tightness of the pumping units **1006**, **1020**, **1044**, and **1056**. Outlet valve **1016** is closed and inlet valve **1004** is opened. Flow sensor **1005** may be positioned before or after inlet valve **1004**. Liquid stored in the pumping unit **1006** is metered out of the chamber **1008** through the flow sensor **1005**. The calibration curve for a known solvent **1136** is provided e.g., (by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in liquid reservoir **1002**, is then processed through a flow sensor **1018** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[**0166**] In the method of calibrating flow sensor **1018**, the pumping system **1000** is characterized to determine the tightness of the pumping units **1006**, **1020**, **1044**, and **1056**. Inlet valve **1004** is closed and outlet valve **1016** is opened. The flow sensor **1018** may be positioned before or after outlet valve **1016**. Liquid stored in the pumping unit **1006** is metered out of the chamber **1008** through the flow sensor **1018**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in reservoir **1002**, is then processed through a flow sensor **1018** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[**0167**] In the method of calibrating flow sensor **1043**, the pumping system **1000** is characterized to determine the tightness of the pumping units **1006**, **1020**, **1044**, and **1056**. Outlet valve **1052** is closed and inlet valve **1042** is opened.

Flow sensor **1043** may be positioned before or after inlet valve **1042**. Liquid stored in the pumping unit **1044** is metered out of the chamber **1046** through the flow sensor **1043**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in reservoir **1040**, is then processed through a flow sensor **1018** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[**0168**] In the method of calibrating flow sensor **1054**, the pumping system **1000** is characterized to determine the tightness of the pumping units **1006**, **1020**, **1044**, and **1056**. Inlet valve **1042** is closed and outlet valve **1052** is opened. Liquid stored in the pumping unit **1044** is metered out of the chamber **1046** through the flow sensor **1054**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in reservoir **1002**, is then processed through a flow sensor **1018** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates.

[**0169**] To calibrate flow sensors **1030**, **1032**, or **1038**, the pumping system **1000** is characterized to determine the tightness of the pumping units **1006**, **1020**, **1044**, and **1056**. A variety of testing methods may be used to test a flow sensor placed on an output of a pumping system **1000**. In one embodiment, the pumping unit **1006** is used to test the flow sensors **1030**, **1032**, or **1038**. In a second embodiment, the pumping unit **1020** is used to test the flow sensors **1018**, **1030**, or **1032**. In a third embodiment, a combination of the pumping unit **1006** and the pumping unit **1020** are used to test the flow sensors **1030**, **1032**, or **1038**.

[**0170**] In one embodiment, a pumping unit in a second channel may be used to calibrate a flow sensor positioned on the output of the second channel. In another embodiment, a pumping unit in a first channel in combination with a pumping unit in the second channel may be used to calibrate a flow sensor positioned on the output of the second channel. For example, when calibrating flow sensor **1038**, piston **1024** may be used in combination with piston **1060** or piston **1060** may be used individually to calibrate flow sensor **1038**. When using piston **1024** in combination with piston **1060**, piston **1024** performs a delivery stroke and piston **1060** performs an intake stroke to calibrate flow sensor **1038**. When using piston **1060** individually to calibrate flow sensor **1038**, piston **1060** performs an intake stroke for backward calibration or piston **1060** performs a delivery stroke for forward calibration. It should be appreciated that a similar approach may be used to calibrate flow sensor **1030** using piston **1060** in combination with piston **1024** or piston **1024** individually.

[**0171**] In one embodiment, pumping unit **1006** is used to test flow sensors **1030**, **1032**, and **1038**. A test is made to determine the tightness of the pumping unit **1006**, pumping unit **1020**, and pumping unit **1056**. The liquid stored in the pumping unit **1006** is metered out of the chamber **1008** through the flow sensor **1018** through the chamber **1022** and through the flow sensors **1030**, **1032**, and/or **1038**. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in reservoir **1002**, is then processed through a flow sensor(s) **1030**, **1032**, and/or **1038** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates. It should be appreciated that a similar approach may be performed to test flow sensors **1030**, **1038**, and **1032** using pumping unit **1044**.

[**0172**] In a second embodiment, pumping unit **1020** is used to test flow sensors **1030**, **1032**, and **1038**. A test is made to determine the tightness of the pumping unit **1020** and pumping unit **1056**. The liquid stored in the pumping unit **1020** is metered out of the chamber **1022** and through the flow sensors **1030**, **1032**, and/or **1038**. It should be appreciated that in the case of flow sensor **1038**, the piston **1060** moves through an intake stroke to draw in solvent as the piston **1024** performs a delivery stroke. The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in reservoir **1002**, is then processed through a flow sensor **1030**, **1032**, and/or **1038** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates. It should be appreciated that a similar method may be used to test flow sensors **1030**, **1038**, and **1032** using pumping unit **1056**.

[**0173**] In a third embodiment, pumping unit **1006** in combination with pumping unit **1020** are used to test flow sensors **1030**, **1032**, and **1038**. A test is made to determine the tightness of the pumping unit **1006** and the pumping unit **1020**. The liquid stored in the pumping unit **1006** is metered out of the chamber **1008** and through the flow sensor **1018** through the chamber **1022** and through the flow sensors **1030**, **1032**, or **1038**. The liquid stored in the pumping unit **1020** is metered out of the chamber **1022** and through the flow sensors **1030**, **1032**, or **1038**. Any combination of pumped solvent from pumping unit **1006** and **1020** is possible. It should be appreciated that in the case of flow sensor **1038**, the piston **1060** moves through an intake stroke to draw in solvent as the piston **1024** performs a delivery stroke.

[**0174**] The calibration curve for a known solvent **1136** is provided (e.g., by the manufacturer). The voltage of a known solvent **1138** at a known flow rate **1142** is identified. An unknown solvent **1140**, such as liquid stored in reservoir **1002**, is then processed through flow sensors **1030**, **1032**, and/or **1038** at a known flow rate **1142**. The calibration factor **1144** is then defined as the ratio of voltage of the unknown solvent **1140** to the voltage of the known solvent **1138**. This method may be performed at different flow rates. It should be appreciated that a similar method may be used to test flow sensors **1030**, **1038**, and **1032** using pumping unit **1044** in combination with pumping unit **1056**.

[**0175**] FIG. **11**E displays a flowchart depicting a method of producing a variable flow rate. FIG. **11**E will be discussed

in conjunction with FIG. **9**A, **9**B, and FIG. **10**. In the method of producing a variable flow rate, flow sensors are positioned at various locations within a pumping system depending on the required flow rate of the pumping system. In one embodiment, the total flow rate of the pumping system is measured at low flow rates. In another embodiment, a portion of the total flow rate is measured at high flow rates. In both cases, leaks in the pumping system are identified and compensated for. The flow sensors are connected within a channel for high flow rates and the flow sensors are connected at the output of a channel for low flow rates.

[**0176**] At step **1140**, a flow rate is identified. The flow rate may be identified by reading a flow sensor, or may be identified based on a metering system, or may be identified by inputting a predefined flow rate into a computer for operations. At step **1142**, a test is performed to determine whether the flow rate is above or below a predefined level. In one embodiment, the predefined level corresponds to the maximum measuring capability of the flow sensor. If the flow rate is below the predefined level, the flow sensor is implemented at the output of the channel as stated at step **1148**. Further, the flow sensor at the output of the channel is used to characterize the total flow measurement of the pumping system as stated at **1150**. If the flow rate is above a predefined level when tested at step **1142**, the flow sensor is implemented within the channel as stated at **1144**. Further, as stated at step **1146**, the flow sensors are used to perform flow measurement, determine leaks, and compensate for leaks. In one embodiment, implementing the flow sensor may include configuring or implementing a flow sensor into a pumping system during operations. For example, when the pumping system is operating with a low flow rate, the flow sensors at the output of the channel may be turned on and operating, and when the pumping system is operating to produce a high flow rate, the flow sensors positioned within the channel of the pumping system may be turned on and operating. It should be appreciated that the same flow sensor can be used for both positions.

[**0177**] The method of producing a variable flow rate presented in FIG. **11**E will be discussed with respect to FIGS. **9**A, **9**B, and **10**. In FIG. **9**A, flow sensor **918** and/or **932** may be implemented in the pumping system **900** when the pumping system **900** is operating to produce a high flow rate and flow sensor **918** and/or **942** may be implemented when the pumping system **900** is operating at a low flow rate. Further, at a high flow rate, flow sensor **918** and/or **932** may indicate a portion of the total flow rate of the pumping system, where the total flow rate is measured at a point denoted by **944**. At a low flow rate, flow sensor **942** is implemented and used to operate the pumping system **900**. Using a method presented in the present application, leaks are detected and compensated for by metering the flow of liquid out of chamber **922**, chamber **936**, or chamber **922** in combination with chamber **936**.

[**0178**] The method of producing a variable flow rate presented in FIG. **11**E will be discussed with respect to FIG. **9**B. In FIG. **9**B, flow sensors **956**, **968**, **976**, and **988** may be implemented in the system when the pumping system **950** is operating to produce a high flow rate, and sensors **956**, **976**, and **994** may be implemented when the pumping system **900** is operating to produce a low flow rate. Further, at a high flow rate, flow sensors **956**, **968**, **976**, and **988** may indicate a portion of the total flow rate of the pumping system, where the total flow rate is measured at a point denoted by **996**. At a low flow rate, flow sensor **994** is implemented and used to operate the pumping system **900**. Using a method presented in the present application, leaks are detected and compensated for by metering the flow of liquid out of chamber **960**, chamber **980**, or chamber **960** in combination with chamber **980**.

[**0179**] In FIG. **10**, flow sensors **1005**, **1018**, **1043**, and/or **1054** may be implemented in pumping system **1000** to measure a high flow rate, and flow sensors **1030**, **1032**, and **1038** may be implemented when the pumping system **1000** is operating to measure a low flow rate. Further, at a high flow rate, flow sensors **1005**, **1018**, **1043**, and **1054** may represent a portion of the total flow rate of the pumping system **1000**, where the total flow rate is the flow rate of liquid at a point denoted by **1034**. At a low flow rate, flow sensors **1030**, **1032**, and/or **1038** are implemented and used to operate the pumping system **1000**. Using methods presented in the instant application, leaks are detected and compensated for by metering the flow of liquid out of chamber **1008**, chamber **1022**, chamber **1046**, chamber **1058**, or any combination of chambers **1008**, **1022**, **1046**, and/or **1058**.

[**0180**] FIG. **12** displays a schematic of a pumping system including pressure sensors. A pumping system **1200** includes a variety of liquids as shown by liquids A, B, C, and D. The liquids A, B, C, and D are stored in a reservoir **1202**. Each liquid (i.e., A, B, C, D) is conveyed on a conveyance **1202**A, **1202**B, **1202**C, and **1202**D. The liquids (i.e., A, B, C, D) are mixed using a proportioning valve **1204**. The liquid (i.e., A, B, C, D) is drawn through an inlet valve **1208** on a conveyance **1205**. A pressure sensor **1206** is positioned on the conveyance **1205** to sense the pressure between the proportioning valve **1204** and the inlet valve **1208**. A pumping unit **1210** is positioned in series with the inlet valve **1208**. The pumping unit **1210** includes a chamber **1212**, a piston **1214**, and a seal **1216**. On the intake stroke of the piston **1214**, liquid fills the chamber **1212** and on the delivery stroke of the piston **1214**, liquid is compressed and forced out of the chamber **1212** through an outlet valve **1220**. A pressure sensor **1209** is position to measure the pressure in the chamber **1212**.

[**0181**] A motor/encoder unit **1218** in conjunction with a computer **1224** are used to adjust the upward and intake stroke of the piston **1214** which meters the flow of liquid through the chamber **1212** by adjusting the intake and expulsion of liquid from the chamber **1212**. A flow sensor **1222** is positioned in series with the outlet valve **1220**. The flow sensor **1222** is capable of measuring the flow of liquid out of pumping unit **1210**.

[**0182**] A variety of methods for determining and compensating for leaks are presented and implemented with the pumping system **1200**. In one embodiment, a method of determining leaks in an inlet valve is presented. In a second embodiment, a method of detecting leaks in an outlet valve is presented. In a third embodiment, a method of determining leaks in a seal/piston combination is presented. In a fourth embodiment, a method of determining leaks in a gradient valve is presented.

[**0183**] FIG. **12**A displays a flow diagram depicting a method of identifying and compensating for leaks using pressure sensors. FIG. **12**A will be discussed in conjunction

with FIG. **12**. In the method depicted in FIG. **12**A, at step **1230**, a chamber is filled with liquid. For example, chamber **1212** is filled with liquid. To fill chamber **1212** with liquid, the outlet valve **1220** is closed, the proportioning valve **1204** is opened, and the inlet valve **1208** is opened. The chamber **1212** then fills with liquid as the piston **1214** performs an intake stroke. Once the chamber **1212** is filled with liquid, the proportioning valve **1204** is closed as shown at **1231**. The inlet valve **1208** and the outlet valve **1220** are also closed as stated at steps **1232** and **1233**. With each valve closed (i.e., **1204**, **1208**, **1220**), compression is performed as shown at step **1234**. During compression, the piston **1214** moves upward (i.e., delivery stroke) to compress the liquid in the chamber **1212** before the outlet valve **1220** is opened. Compressing liquid in the chamber **1212** increases the pressure in the chamber **1212**. When the pumping system **1200** reaches steady state (i.e., all the components have settled), the pressure is measured. The pressure sensor **1206** is monitored for a change in pressure as stated at **1235**. If an increase in pressure is determined, the increase in pressure signals a flow of liquid back through the inlet valve **1208** as a result of a leak in the inlet valve **1208**. In addition, based on the amount of pressure increase in the pressure sensor **1206**, the amount of the leak in the inlet valve **1208** may be calculated as stated at **1236**. In one embodiment of the present invention, the amount of leak in the inlet valve **1206** is calculated using the volume between the proportioning valve **1204** and the inlet valve **1206**, the compressibility factor of the liquid and the pressure increase. Once the amount of the leak has been determined, adjustments may be made in the pumping system **1200** to accommodate for the leak as stated at **1237**. For example, using the piston **1214**, the motor/encoder unit **1218**, and the computer **1224**, metering may be performed to compensate for the leak.

[**0184**] FIG. **12**B displays a flow diagram depicting a method of identifying and compensating for leaks using flow sensors. FIG. **12**B will be discussed in conjunction with FIG. **12**. In the method depicted in FIG. **12**B, a proportioning valve is opened as stated at **1240**. An inlet valve is opened as stated at **1241**, and an outlet valve is closed as stated at **1242**. A first piston in a first pumping unit performs an intake stroke as stated at **1243**. It should be appreciated that in a second embodiment, the method depicted in FIG. **12**B may be performed without performing the intake stroke as stated at step **1243**. Opening the proportioning valve as stated at **1240**, opening the inlet valve as stated at **1241**, and closing the outlet valve as stated at **1242** will result in a backflow of liquid provided that the pressure after the outlet valve is higher than the pressure within chamber **1212**. A flow sensor is used to monitor the back flow of liquid as stated at **1244**. The back flow is used to calculate the amount of a leak as stated at **1245**. In any case, metering is performed, e.g., with a second piston (not shown in FIG. **12**) leaks can be compensated for as stated at **1246**.

[**0185**] The method depicted in the flow diagram of FIG. **12**B will be discussed with respect to the pumping system depicted in FIG. **12**. As stated at steps **1240**, **1241**, and **1242**, a proportioning valve and an inlet valve are opened and an outlet valve is closed. For example, using FIG. **12**, the proportioning valve **1204** is opened, the inlet valve **1208** is opened, and the outlet valve **1220** is closed. At step **1243**, an intake stroke is performed. For example, piston **1214** positioned in pumping unit **1210** performs an intake stroke. At step **1244**, a flow sensor, such as flow sensor **1222**, positioned before or after the outlet valve **1220**, is monitored to detect a back flow **1226** of liquid. If liquid is detected by flow sensor **1222**, the liquid indicates that there is a leak in the outlet valve **1220**. Once the leak has been determined, the amount of liquid flowing through the flow sensor **1222** may be used to calculate the amount of the leak as stated at **1245**. In one embodiment, it should be appreciated that the flow sensor is measuring the amount of the leak directly. If a leak occurs, the new-metered flow rate with a piston after the flow sensor (not shown in FIG. **12**) is equivalent to the metered flow, which is equal to the nominal flow plus the leak. Once the amount of the leak is calculated, metering may be performed to compensate for the leak as stated at **1246**. Metering may include operating, e.g., a second piston of a serial pumping system, a motor/encoder unit responsible for moving that second pumping piston, and a corresponding computer (not shown in FIG. **12**) to compensate for the amount of the leak.

[**0186**] FIG. **12**C displays an embodiment of a flow diagram depicting a method of detecting a leak in a chamber, such as chamber **1212** of FIG. **12**. FIG. **12**C will be discussed in conjunction with FIG. **12**. The method depicted in the flow diagram of FIG. **12**C may be used to detect leaks in a piston/seal **1214**/**1213** combination, the leak in an inlet valve **1208**, the leak in an outlet valve **1220**, a leaky fitting, etc.

[**0187**] At step **1250** of FIG. **12**C, a chamber positioned in a pumping unit is checked for tightness. For example, chamber **1212** positioned in pumping unit **1210** is checked for tightness. At step **1251**, the chamber is pressurized. In one embodiment, piston **1214** is moved through a portion of a delivery stroke to pressurize liquid in chamber **1212**. At step **1252**, stopping the movement of the piston **1214** stops the pressurization. At step **1253**, time is allotted to wait for the settling effects and pressure is monitored over a period of time. For example, time is allotted to wait for the settling effects of the pumping unit **1210**. After settling is completed, the pressure sensor **1209** is used to monitor the pressure in the chamber **1212** over a period of time. At step **1254**, if the pressure has not dropped below a predefined value, then there is no leak as stated at **1255**. At step **1254**, if the pressure has dropped below a predefined value, then a leak is determined as stated at **1256**. The leak may be determined using two methods. In one embodiment, at step **1257**, a leak is determined by a pressure drop over time. As a result, the leak equals the internal volume times solvent compressibility times the pressure drop, where the internal volume is the volume of the liquid in the chamber **1212**, the solvent compressibility is the compression of liquid in the chamber **1212**, and the pressure drop is the pressure reading on the pressure sensor **1209**. In an alternate embodiment, the leak is determined by moving the piston **1214** upward until the pressure is stable as stated at **1258**. Using FIG. **12**, this would include moving piston **1214** upward through a portion of a delivery stroke until the pressure registered by pressure sensor **1209** is stable. During the partial delivery stroke, the metered liquid or solvent may be determined using the motor/encoder system **1218** and the computer **1224**. The leak will then equal the metered solvent as stated at **1259**.

[**0188**] FIG. **12**D displays an embodiment of a flow diagram depicting a method of detecting a blocked conveyance (i.e., a blocked filter at a conveyance inlet). FIG. **12**D will be discussed in conjunction with FIG. **12**. At step **1260**, the

pressure drop is determined during the intake of liquid through each conveyance or tube (i.e., **1202**A, **1202**B, **1202**C, **1202**D). At step **1261**, the limits of the pressure drop are defined for each conveyance. At step **1262**, the pressure drop is monitored as liquid is conveyed through each tube. If the pressure does not drop below a predefined level as stated at step **1263**, no blockage is detected as stated at step **1264**. If the pressure does drop below a predefined level as stated at step **1263**, blockage is detected as stated at step **1265**. In one embodiment, adjustments may be made to compensate for blockage as stated at **1266**. For example, in the case of a partial blockage, the intake stroke of piston **1214** may be adjusted to draw in liquid with lower speed to compensate for the blockage (e.g., avoid generation of gas bubbles).

[**0189**] The flow diagram of FIG. **12**D will be discussed in conjunction with the pumping system **1200** depicted in FIG. **12**. In FIG. **12**, pressure sensor **1206** may be used to calibrate the inlet pressure for conveyances **1202**A, **1202**B, **1202**C, and **1202**D. To calibrate the inlet pressure for each conveyance (**1202**A, **1202**B, **1202**C, and **1202**D), as the inlet valve **1208** is opened and the piston **1214** intakes liquid (i.e., A, B, C, D), pressure is measured as the liquid (i.e., A, B, C, D) is conveyed past the pressure sensor **1206**. For example, when liquid (i.e., A) flows through conveyance **1202**A via conveyance **1205** to inlet valve **1208**, the pressure is measured. When liquid (i.e., B) flows through conveyance **1202**B the to conveyance **1205**, the pressure is measured. When liquid (i.e., C) flows through conveyance **1202**C to conveyance **1205**, the pressure is measured. When liquid (i.e., D) flows through conveyance **1202**D to conveyance **1205**, the pressure is measured. Using the aforementioned techniques, a pressure drop is determined as stated at **1260** of FIG. **12**D. The limits of the pressure drop are defined as stated at **1261** of FIG. **12**D. At step **1262**, the pressure drop is monitored during the intake phase of the solvent using pressure sensor **1206**. During operation, at step **1263**, a test is made to determine if the pressure drop is below a predefined value (i.e., level). If the pressure has dropped below a predefined value (i.e., Yes), then this signals that there is no blockage. If the pressure has not dropped below a predefined value (i.e., No), this signals a partial or total blockage. In one embodiment, the blockage may occur in conveyances **1202**A, **1202**B, **1202**C and/or **1202**D. Once blockage has been detected, activities may be performed to compensate for a partial blockage as stated at **1266**. For example, piston **1214** may perform an adjusted intake stroke to ensure the correct volume of liquid is brought in across the conveyance. For example, in one embodiment, the intake stroke speed is reduced to avoid the generation of gas bubbles.

[**0190**] FIG. **12**E displays an embodiment of a flow diagram depicting a method of detecting a leak in a proportioning valve. FIG. **12**F displays an embodiment of a flow diagram depicting a method of testing the tightness of a proportioning valve. Both FIGS. **12**E and **12**F will be discussed in conjunction with FIG. **12**. In one embodiment of detecting a leak in a proportioning valve, an on/off valve, such as a proportioning valve **1204**, is closed. If more channels or conveyances (i.e., liquids) are connected (A, B, C, D), all the channels or conveyance are closed. A piston, such as the piston **1214**, is moved to intake liquid into the chamber **1212**. Pressure is measured. For example, the pressure sensor **1206** may measure the pressure on conveyance **1205**. In one embodiment, when performing an intake stroke with the piston **1214** (i.e., inlet valve opened and outlet valve closed), the pressure on conveyance **1205** decreases to a level below atmospheric pressure. The piston stops and the pressure is monitored. After waiting a time for settling effects, the pressure is constant. In the case of a leak in the proportioning valve, the pressure will increased to atmospheric pressure. It should be appreciated that the pumping unit must be tested for tightness before the test described above is performed.

[**0191**] In another embodiment, the tightness of the proportioning valve is tested. First, the pumping unit (i.e., piston/chamber) is tested for tightness as described above. Afterwards, all of the channels (i.e., each conveyance) of the proportioning valve is closed, the inlet valve is opened and the outlet valve is closed. The piston moves upward to increase the pressure in the conveyance **1205** to a level above atmospheric pressure. The piston stops, waiting a time for settling effects and monitoring the pressure. If the proportioning valve **1204** is tight, the pressure is constant and remains above a predefined level. If leaky, the pressure decreases to atmospheric pressure over time.

[**0192**] In both embodiments presented above, the amount of leak is calculated by the volume of liquid between the proportioning valve **1204** and the inlet valve **1208**, the compressibility factor of the liquid, and the pressure change over time. For example, in one embodiment, the leak is equal to the volume times the compressibility of liquid times the pressure change.

[**0193**] In another embodiment, the chamber **1212** is checked for tightness using a pressure sensor **1206** on a conveyance, such as conveyance **1205**. The inlet valve **1208** is opened, the outlet valve **1220** is closed, the proportioning valve **1204** is closed completely (all channels), the conveyance **1205** is pressurized by moving the piston **1214** upwards. The pressure is monitored. A pressure level is predefined. Adapting the speed of the piston **1214** to keep the pressure constant controls the pressure. The pumped liquid required to keep that pressure constant on conveyance **1205** is equivalent to the amount of the leak. It should be appreciated that the pressure registered using pressure sensor **1206** may be above or below the atmospheric pressure. In the first case, the piston **1214** is moved upward. In the second case, the piston **1214** is moved downward. The first case, where the pressure is above atmospheric pressure, this may signal a liquid leak from internal (i.e., inside the chamber **1212**) to external (i.e., outside the chamber **1212**). In the second case, where the pressure is below atmospheric pressure, this may signal an air leak from external (i.e., outside the chamber **1212**) to internal (i.e., inside the chamber **1212**). In either case, the metered flow equals the leak (i.e., at constant pressure).

[**0194**] FIG. **12**E displays an embodiment of a flow diagram depicting a method of detecting a leak in a proportioning valve. FIG. **12**F displays an embodiment of a flow diagram depicting a method of testing the tightness of a proportioning valve. FIG. **12**G displays an embodiment of a flow diagram depicting a method of testing a chamber disposed in a pumping unit for tightness. FIGS. **12**E and **12**F will be discussed in conjunction with FIG. **12**.

[**0195**] At **1270** of FIG. **12**E, a valve, such as a gradient valve or proportioning valve **1204**, is checked to determine

leaks. For example, proportioning valve **1204** is checked for leaks. At step **1271**, an outlet valve, such as outlet valve **1220**, is closed; an inlet valve, such as inlet valve **1208**, is opened; and a valve, such as proportioning valve **1204**, is closed. At step **1272**, the chamber **1212** is pressurized. In one embodiment, pressurizing the chamber **1212** includes moving the piston **1214** downward through a partial intake stroke. When the piston **1214** moves downward through a partial intake stroke, the pressure on conveyance **1205** decreases to a level below atmospheric pressure. At step **1273**, the piston **1214** is stopped to discontinue the pressurization of the conveyance **1205**. At step **1274**, time is allowed to wait for settling effects. At step **1275**, the pressure is monitored on conveyance **1205** using pressure sensor **1206**. At step **1276**, a test is made to determine if the pressure has increased above a predefined level and if so then there is no leak in proportioning valve **1204** as stated at **1277**. If the pressure does increase above a predefined value, then a leak in proportioning valve **1204** may be determined as stated at **1278**. The leak may be determined in two ways. In one embodiment, the leak is calculated by the increase in pressure over time as shown at **1279**. In this case, the calculated leak equals the internal volume times the solvent compressibility times the pressure increase. In a second embodiment, the leak is determined by moving the piston **1214** downward as stated at **1280** until the pressure measured by pressure sensor **1206** is stable. The motor/encoder unit **1218** in conjunction with the computer **1224** are then used to determine the metered solvent from the downward movement of the piston **1214** and the leak is equal to the metered solvent as stated at **1281**.

[**0196**] At **1285** of FIG. **12**F, a valve, such as proportioning valve **1204**, is tested for tightness. At step **1286**, an outlet valve, such as outlet valve **1220**, is closed; an inlet valve, such as inlet valve **1208**, is opened; and a proportioning valve, such as proportioning valve **1204**, is closed. At step **1287**, the chamber **1212** is pressurized. In addition, since inlet valve **1208** is opened, conveyance **1205** is pressurized. In one embodiment, pressurizing the chamber **1212** includes moving the piston **1214** upward through a partial delivery stroke. When the piston **1214** moves upward through a partial intake stroke, the pressure on conveyance **1205** is increased to a level above atmospheric pressure. At step **1288**, the piston **1214** is stopped to stop the pressurization of the chamber **1212** and the conveyance **1205**. At step **1289**, time is allowed to wait for settling effects. At step **1290**, the pressure is monitored on conveyance **1205** using pressure sensor **1206**. At step **1291**, a test is made to determine if the pressure has decreased below a predefined level as stated at **1291**. If the pressure has not dropped below a predefined level pressure, then no leak has been determined as stated at **1292**. If the pressure has dropped below a predefined level pressure, then a leak may be determined as stated at **1294**. The leak may be determined in two ways. In one embodiment, the leak is calculated by the decrease in pressure over time as shown at **1293**. In this case, the calculated leak equals the internal volume times the solvent compressibility times the pressure drop. In a second embodiment, the leak is determined by moving the piston **1214** upward as stated at **1295** until the pressure measured by pressure sensor **1206** is stable. The motor/encoder system **1218** in conjunction with the computer are then used to determine the metered solvent from the upward movement of the piston **1214** and the leak equals the metered solvent as stated at **1296**.

[**0197**] A method of testing a chamber for tightness is displayed in FIG. **12**G. In another embodiment, the chamber **1212** is checked for tightness using a pressure sensor **1206** positioned in a conveyance, such as conveyance **1205**. In the method at step **1290**G, an inlet valve, such as inlet valve **1208**, is opened, the outlet valve, such as outlet valve **1220**, is closed, and the proportioning valve, such as proportioning valve **1204**, is closed completely (all channels). The conveyance **1205** is pressurized as stated at **1291**G by moving the piston **1214** upwards. The pressure on conveyance **1205** is monitored. The pressure is monitored using pressure sensor **1206**. A pressure level is predefined. The pressure is controlled by adapting the speed of the piston **1214** to keep the pressure constant as stated at **1292**G. The pumped liquid required to keep the pressure constant on conveyance **1205** is equivalent to the amount of the leak. It should be appreciated that the pressure registered using pressure sensor **1205** may be below or above the atmospheric pressure. At **1293**G, a test is made to determine if the pressure is above or below atmospheric pressure. If the pressure is above atmospheric pressure, piston **1214** is moved upward as stated at **1294**G. A pressure above atmospheric pressure signals a liquid leak from internal (i.e., inside the chamber **1212**) to external (i.e., outside the chamber **1212**) and steps may be taken to determine the leak as stated at **1295**G. In one embodiment, the metered flow equals the leak (i.e., at constant pressure). If the pressure is below atmospheric pressure, piston **1214** is moved downward as stated at **1296**G. Where the pressure is below atmospheric pressure, this may signal an air leak from external (i.e., outside the chamber **1212**) to internal (i.e., inside the chamber **1212**) and steps may be taken to determine the leak from external to internal as stated at **1297**G. In one embodiment, the metered flow equals the leak (i.e., at constant pressure).

[**0198**] FIG. **13** displays a schematic diagram of a single-channel pumping system **1300** including flow sensors. The single-channel pumping system **1300** includes a reservoir **1302** storing a variety of liquids as shown by liquids A, B, C, and D. A switch, such as a proportioning valve **1304**, is connected in series with a flow sensor **1306**. The flow sensor **1306** is connected in series with an inlet valve **1308**. The inlet valve **1308** is in series with a pumping unit **1311**. The pumping unit **1311** includes a chamber **1312** and a piston **1314**. The pumping unit **1311** is further in series with a chamber **1318**. In one embodiment, flow sensor **1313** is positioned between pumping unit **1311** and pumping unit **1319**. The pumping unit **1319** includes a chamber **1318** and a piston **1320**. The pumping unit **1311** is connected to a motor/encoder system **1316** and the pumping unit **1319** is connected and controlled by a motor/encoder system **1322**. Both the motor/encoder system **1316** and the motor/encoder system **1322** are connected to and controlled by computer **1324**.

[**0199**] The liquids (i.e., A, B, C, D) are mixed in a proportioning valve **1304** and conveyed through a flow sensor **1306** to an inlet valve **1308**. On the intake stroke of the piston **1314**, liquid (i.e., A, B, C, D) fills the chamber **1312** and on the delivery stroke of the piston **1314**, liquid (i.e., A, B, C, D) is compressed and forced out of the chamber **1312** through the outlet valve **1310**. A motor/encoder system **1316** and a computer **1324** are used to meter the flow of liquid (i.e., A, B, C, D) through the pumping unit **1311** by adjusting the upward and intake stroke of the piston **1314** to adjust the intake and expulsion of liquid (i.e., A, B,

C, D) from the chamber **1312**. The outlet valve **1310** is positioned to allow liquid (i.e., A, B, C, D) to flow between the pumping unit **1311** and the pumping unit **1319**, which is in series with the pumping unit **1311**. A pumping unit **1319** includes a piston **1320**. Liquid (i.e., A, B, C, D) is received from the chamber **1312** into the chamber **1318**. The flow of liquid (i.e., A, B, C, D) between the pumping unit **1311** and the pumping unit **1319** is measured by a flow sensor **1313** positioned between the two pumping units **1311** and **1319**. Liquid (i.e., A, B, C, D) fills the chamber **1318** and on the delivery stroke of the piston **1320**, liquid (i.e., A, B, C, D) is forced out of the chamber **1318**. A motor/encoder system **1322** and a computer **1324** are used to adjust the upward and intake stroke of the piston **1320** to adjust the intake and expulsion of liquid (i.e., A, B, C, D) from the chamber **1318**. Lastly, liquid (i.e., A, B, C, D) is delivered to the remainder of the chromatography system as shown at **1326**.

[**0200**] FIG. **13**A displays an embodiment of a flow diagram depicting a method of detecting a leak in a gradient valve. FIG. **13**A will be discussed in conjunction with FIG. **13**. At step **1340**, a flow sensor positioned between a proportioning valve **1304** and an inlet valve **1308** is calibrated for each liquid (i.e., A, B, C, D) stored in a reservoir **1302**. For example, the flow sensor **1306** positioned between the proportioning valve **1304** and the inlet valve **1308** is calibrated for each liquid (i.e., A, B, C, D) stored in the reservoir **1302**. At step **1341**, the proportioning valve **1304** is closed, the inlet valve **1308** is opened, and the outlet valve **1310** is closed. At step **1342**, the piston **1314** performs a portion of an intake stroke to attempt to intake liquid (i.e., A, B, C, D) from the proportioning valve **1304**. At **1343**, the flow sensor **1306** is used to measure the flow of liquid (i.e., A, B, C, D). If there is a leak in the proportioning valve **1304**, liquid (i.e., A, B, C, D) flows through the flow sensor **1306** and a leak is determined as stated at **1344**.

[**0201**] FIG. **13**B displays an embodiment of a flow diagram depicting a method of detecting a leak in an inlet valve. FIG. **13**B will be discussed in conjunction with FIG. **13**. At step **1346**, the flow sensor **1306** is calibrated for each liquid (i.e., A, B, C, D) stored in the reservoir **1302**. At step **1347**, the chamber **1312** is filled with liquid (i.e., A, B, C, D). To fill the chamber **1312** with liquid (i.e., A, B, C, D), the proportioning valve **1304** is opened, the inlet valve **1308** is opened, and the outlet valve **1310** is closed. The piston **1314** then performs an intake stroke to fill the chamber **1312**. Once the chamber **1312** is filled, the inlet valve **1308** is closed. The piston **1314** then moves through a delivery stroke to compress the liquid (i.e., A, B, C, D) and pressurize the chamber **1312** as stated at step **1348**. At step **1349**, an attempt is then made to measure liquid (i.e., A, B, C, D) in the flow sensor **1306**. If a flow of liquid (i.e., A, B, C, D) is measured in flow sensor **1306** as stated at step **1349**, the flow of liquid (i.e., A, B, C, D) is an indication that the inlet valve **1308** has a leak and a leak is determined as stated at step **1350**. Once the leak is determined, metering may be performed to compensate for the leak as stated at step **1351**.

[**0202**] In an alternate embodiment of the present invention, a flow diagram in FIG. **13**B may be used to determine a leak in outlet valve **1310**. FIG. **13**B will be discussed in conjunction with FIG. **13**. At step **1346**, the flow sensor **1313** is calibrated for each liquid (i.e., A, B, C, D) stored in the liquid reservoir **1302**. It should be appreciated that the flow sensor **1313** may be positioned before the outlet valve **1310** or the flow sensor **1313** may be positioned after the outlet valve **1310**. At step **1347**, the chamber **1318** is filled with liquid (i.e., A, B, C, D). To fill the chamber **1318** with liquid (i.e., A, B, C, D), while the inlet valve **1308** is closed and the outlet valve **1310** is opened, the piston **1314** moves upward through a delivery stroke and the piston **1320** moves downward through an intake stroke. Performing the intake stroke fills the chamber **1318**. Once the chamber **1318** is filled, the outlet valve **1310** is closed. The piston **1320** then moves through a delivery (i.e., upward) stroke. At step **1349**, an attempt is then made to measure liquid (i.e., A, B, C, D) in the flow sensor **1313**. If flow (i.e., back flow from chamber **1318**) is measured in flow sensor **1313** as stated at step **1349**, the back flow is an indication that the outlet valve **1310** has a leak and a leak is determined as stated at step **1350**. It should be appreciated that the leak may be determined using any of the methods presented for determining leaks. Once the leak is determined, metering may be performed to compensate for the leak as stated at step **1351**.

[**0203**] FIG. **13**C presents a flow diagram of a method of performing a smooth intake stroke. FIG. **13**C will be discussed in conjunction with FIG. **13**. At step **1352**, a pumping system, such as single-channel pumping system **1300**, is operating. During operation, the proportioning valve **1304** allows liquid (i.e., A, B, C, D) from reservoir **1302** to be delivered to the pumping unit **1311**. At step **1353**, a flow sensor, such as the flow sensor **1306**, positioned between the proportioning valve **1304** and the pumping unit **1311** is used to measure the intake flow. In another embodiment, the flow sensor is not configured in the system. In one embodiment, the intake flow of liquid is not continuous flow and has discontinuities or increases and decreases in volume or flow. At step **1354**, the motor/encoder system **1316** is used to meter the intake flow to adjust for any discontinuities in the intake flow. Metering the intake flow includes adjusting the speed and/or timing of the piston **1314** using the motor/encoder system **1316** in conjunction with the computer **1324**.

[**0204**] FIG. **13**D presents a graph depicting a method of metering the intake flow to adjust for discontinuities in the intake flow. As a result of metering, a smooth and highly precise intake flow may be accomplished. The individual liquids (A, B, C, and D) accelerate and facilitate smooth transitions when the proportioning valve **1304** is switched. FIG. **13**D will be discussed in conjunction with FIG. **13**. FIG. **13**D presents a graph of the position of the piston **1314** as a function of time. The upper limit of piston movement known as the upper dead center (UDC) and the lower limit of piston movement known as the lower dead center (LDC) are shown on the Y-axis of the graph. The liquid intake period is shown as **1360** and the liquid delivery period is shown as **1362** (i.e., for part of the delivery cycle). The portion of the graph associated with the intake of liquid A is shown as **1364**, the portion of the graph associated with the intake of liquid B is shown as **1366**, the portion of the graph associated with intake of liquid C is shown as **1368**, and the portion of the graph associated with the intake of liquid D is shown as **1370**. In addition, the initial compression and the final delivery of liquid, which occurs during the liquid delivery period **1362** is shown as **1372** and **1374**, respectively. As shown in FIG. **13**D, the piston **1314** is moving in a non-uniform manner to vary intake speed and the position of the piston **1314** as shown by the portion of the graph associated with the intake of liquid A shown as **1364**, the

portion of the graph associated with the intake of liquid B shown as **1366**, the portion of the graph associated with the intake of liquid C shown as **1368**, and the portion of the graph associated with the intake of liquid D shown as **1370**. As a result, no discontinuities in the intake of the liquid (i.e., A, B, C, D) are seen by the pumping system **1300** when the proportioning valve **1304** switches between liquids in the reservoir **1302**. Further, more precise metering is accomplished when no liquid or less liquid is drawn by piston **1314** while activating the switching or proportioning valve **1304**. The corresponding liquids (i.e., A, B, C, D) are accelerated and decelerated very smoothly.

[**0205**] FIG. **14** depicts a pumping system **1400**. A channel **1401** and **1402** are shown in the pumping system **1400**. A liquid may be stored in reservoir **1403**. An inlet valve **1404** is positioned in series with a pumping unit **1405**. The pumping unit **1405** includes a chamber **1406** and a piston **1408** capable of reciprocating motion within the chamber **1406**. The pumping unit **1405** may be configured with a pressure sensor **1407**, which is positioned in chamber **1406**, to detect the pressure in chamber **1406**. An outlet valve **1424** is positioned in series with the pumping unit **1405** and is positioned on an oppositely disposed side of the chamber **1406** from the inlet valve **1404**. A motor/encoder system **1414** is connected to the pumping unit **1405** and controls the reciprocating motion of the piston **1408**. A computer **1417** controls the motor/encoder system **1414**.

[**0206**] A pumping unit **1427** is in series with the pumping unit **1405**. The pumping unit **1427** includes a chamber **1428** and a piston **1420** capable of reciprocating motion within the chamber **1428**. The pumping system **1400** may be configured with a flow sensor **1425** positioned between the pumping unit **1405** and the pumping unit **1427**. It should be appreciated that the flow sensor **1425** may be positioned before or after the outlet valve **1424**. The pumping system **1400** may be configured with a flow sensor **1429** positioned on output **1423** of the channel **1401**. A motor/encoder unit **1415** is connected to the pumping unit **1427** and controls the reciprocating motion of the piston **1420**. Computer **1417** controls the motor/encoder unit **1415**.

[**0207**] A liquid may be stored in a reservoir **1432**. An inlet valve **1434** is positioned in series with a pumping unit **1435**. The pumping unit **1435** includes a chamber **1436** and a piston **1438** capable of reciprocating motion within the chamber **1436**. The pumping system **1400** may be configured with a pressure sensor **1431** positioned in the chamber **1436**. An outlet valve **1442** is in series with the pumping unit **1435** and is positioned on an oppositely disposed side of the chamber **1436** from the inlet valve **1434**. A motor/encoder unit **1440** is connected to the pumping unit **1435** and controls the reciprocating motion of the piston **1438**. A computer **1417** controls the motor/encoder system **1440**.

[**0208**] A pumping unit **1447** is in series with the pumping unit **1427**. The pumping system **1400** may include a flow sensor **1430** positioned between the pumping unit **1435** and the pumping unit **1447**. The pumping unit **1447** includes a chamber **1446** and a piston **1448** capable of reciprocating motion within the chamber **1446**. The pumping system **1400** may include a flow sensor **1433** positioned on the output **1443** of the channel **1402**. A motor/encoder unit **1450** is connected to the pumping unit **1447** and controls the reciprocating motion of the piston **1448**. A computer **1417** controls the motor/encoder unit **1450**. Lastly, a pressure sensor **1445** is positioned on the output **1455** of the pumping system **1400**.

[**0209**] FIG. **14**A displays a flow diagram depicting a method of operating a pumping channel. In addition, alternate embodiments of the method of operating a pumping channel are presented. For example, a method of detecting a leak in a first piston in a channel is presented. A method of detecting a leak in a second piston in a channel is presented. A method of detecting a leak when the pumping system **1400** is operating at low flow rates (i.e., within the range of the flow sensor) is presented. A method of detecting a leak when a pumping system **1400** is operating outside of the range of the flow sensor (i.e., high flow rates) is presented. FIG. **14**A will be discussed in conjunction with FIG. **14**.

[**0210**] In addition to the various embodiments, several parameters are defined for discussion purposes. In one embodiment, a nominal flow rate may be defined as a flow rate requested at the output **1455** of the pumping system. The nominal flow rate may be input by a user into computer **1417** and the pumping system **1400** may coordinate between the various pumping units (i.e., **1407**, **1427**, **1435**, and **1447**) within the pumping system **1400** to produce the nominal flow rate. In one embodiment, the measured flow rate may be defined as the flow rate measured by a flow sensor, such as flow sensors **1425**, **1429**, **1430**, and **1433**. Lastly, in one embodiment, a metered flow rate may be defined as a flow rate produced or recorded by a motor/encoder system **1414**, motor/encoder system **1415**, motor/encoder system **1440**, motor/encoder system **1450**. In one embodiment of the present invention, a leak is equivalent to the metered flow rate minus the measured flow rate (i.e., leak=metered flow rate−measured flow rate).

[**0211**] A method of determining leaks is presented in FIG. **14**A. At step **1440**, the flow rate of a pumping unit (i.e., **1405**, **1427**, **1435**, **1447**) is determined. The flow rate may be determined by measuring, metering, etc. Further, the flow rate may be determined at various positions within the pumping system **1400**. At step **1441**, a change in the flow rate is determined. In one embodiment, a change in the flow rate is determined by measuring the change with a flow sensor (i.e., **1425**, **1429**, **1430**, **1433**). At step **1442**, a leak is identified and calculated in the channel. At step **1443**, compensation is made for the leak.

[**0212**] A method of determining a leak in a pumping unit in a channel when the pumping unit is operating within the range of a flow sensor is presented. The method will be discussed using FIG. **14** in combination with the flow diagram presented in FIG. **14**A. First, a constant flow rate is metered (i.e., used) for as the nominal flow rate. At **1440** of FIG. **14**A, the flow rate is determined. For example, the flow sensor **1425** or the flow sensor **1430** is used to determine the measured flow rate of pumping unit **1405** or **1435**. Since the flow sensor **1425** and the sensor **1430** are connected to the computer **1417**, the computer **1417** is capable of recording the flow rate detected by each sensor (i.e., **1425**, **1430**) over time. At step **1441**, each flow sensor (i.e., **1425**, **1430**) is monitored to identify a change in the flow rate. At step **1442**, a change in the flow rate signifies a leak in a pumping unit. In one embodiment, this assumes a constant metered flow rate. At step **1443**, compensation is made for the leak in the

channel. In a second embodiment, at **1440** of FIG. **14**A, the flow rate is determined. For example, the flow sensor **1425** or the flow sensor **1430** is used to determine the measured flow rate of pumping unit. At step **1441**, the metered flow rate is determined. For example, motor/encoder system **1414** and motor/encoder system **1440** are each used in combination with computer **1417** to determine a metered flow rate for each pumping unit (i.e., **1405** and **1435**, respectively). At step **1442**, a leak is identified and calculated. In one embodiment, the leak equals the metered flow rate minus the measured flow rate (i.e., leak=metered−measured). Once the leak has been calculated, at step **1443**, compensation is made for the leak. Compensation for the leak may include operating pumping units **1405** and **1435** to deliver additional liquid, which is equivalent to the amount of the leak.

[**0213**] In another embodiment of the present invention, a method of determining a leak in a channel when the output of the channel is within the operating range of a flow sensor is presented. The method will be discussed using FIG. **14** in combination with the flow diagram presented in FIG. **14**A. At **1440** of FIG. **14**A, the flow rate is determined. For example, the flow sensor **1429** or the flow sensor **1433** is used to determine the measured flow rate of channels **1401** and **1402**, respectively. Since the flow sensor **1429** and the flow sensor **1433** are connected to the computer **1417**, the computer **1417** is capable of recording the flow rate detected by each flow sensor (i.e., **1429**, **1433**) over time. At step **1441**, each flow sensor (i.e., **1429**, **1433**) is monitored to identify a change in the flow rate. In one embodiment, this assumes a constant metered flow rate. At step **1442**, a change in the flow rate signifies a leak in the channel (i.e., **1401**, **1402**). At step **1443**, compensation is made for the leak in the channel (i.e., **1401**, **1402**). In one embodiment, compensating for the leak in the channel (i.e., **1401**, **1402**) may include operating a pumping unit (**1405**, **1435**) in the channel (i.e., **1401**, **1402**)) to output liquid equal to the amount of the leak. In a second embodiment, compensating for the leak in the channel may include operating a pumping unit (i.e., **1427**, **1447**) in the channel to output liquid equal to the amount of the leak. In a third embodiment, compensating for the leak in the channel may include operating pumping units (**1405**, **1435**) in the channel in combination with a pumping unit (**1427**, **1447**) in a channel to output liquid equal to the amount of the leak. It should be appreciated that the foregoing method may be extended to any amount of pumping units configured in a channel.

[**0214**] In a second embodiment of determining a leak in a channel when the output of the channel is within the operating range of a flow sensor, at **1440** of FIG. **14**A, the flow rate is determined. For example, the flow sensor **1429** or the flow sensor **1433** may be used to determine the measured flow rate of channel **1401**. At step **1441**, the metered flow rate is determined for each pumping unit (i.e., **1405**, **1427**, **1435**, **1447**). For example, motor/encoder system **1414**, motor/encoder system **1440**, motor/encoder system **1415**, motor/encoder system **1450** are each used in combination with computer **1417** to determine a metered flow rate for each pumping unit (i.e., **1405**, **1435**, **1427**, **1447**, respectively). At step **1442**, a leak is identified and calculated. In one embodiment, the leak equals the metered flow rate minus the measured flow rate (i.e., leak=metered−measured). Once the leak has been calculated, at step **1443**, compensation is made for the leak. Compensation for the leak may include operating pumping units **1405**, **1427**, **1435**, and **1447** to deliver additional liquid, which is equivalent to the amount of the leak calculated for each channel (i.e., **1401**, **1402**).

[**0215**] In a number of alternate embodiments, once a leak has been determined, a number of methods are presented for compensating for the leak in the pumping system **1400** as stated in step **1443**. For example, individual metering methods may be implemented or integrated metering methods may be implemented. With an individual metering method, the flow of liquid through a single pumping unit (i.e., **1405**, **1427**, **1435**, **1447**) may be metered to compensate for the leak in the channel (i.e., **1401**, **1402**). Each pumping unit (i.e., **1405**, **1427**, **1435**, **1447**) in a channel (i.e., **1401**, **1402**) may be individually adjusted to compensate for a leak in the channel (i.e., **1401**, **1402**). For example, pumping units **1405** and **1427** may be individually adjusted to meter liquid through the pumping unit (i.e., **1405**, **1427**) and consequently compensate for the leak in the channel **1401**. In a similar manner, pumping units **1435** and **1447** may be individually adjusted to meter liquid through the pumping unit (i.e., **1435**, **1447**) and consequently compensate for the leak in the channel **1402**. In the alternative, integrated metering methods may be implemented. For example, if there is a leak in the channel **1401**, the pumping unit **1405** and the pumping unit **1427** may operate in a coordinated fashion to compensate for the leak.

[**0216**] FIG. **15**A displays a flow diagram depicting a method of determining a leak in a piston seal with a flow sensor positioned between two pumping units in a channel of a pumping system. FIG. **15**A will be discussed in conjunction with FIG. **14** and FIG. **15**B. The flow diagram of FIG. **15**A depicts a method of determining a leak in a seal **1421**, in piston **1420**, using sensor **1425**, and/or determining a leak in a seal **1449** in piston **1448** using sensor **1430**. In FIG. **15**A, at step **1560**, each pumping unit (i.e., **1405**, **1427**, **1435**, **1447**) within each channel (i.e., **1401**, **1402**) is operating. Therefore, the pumping unit **1405**, the pumping unit **1427**, the pumping unit **1435**, and the pumping unit **1447** operate. At step **1561** of FIG. **15**A, the flow variations of each channel, such as the channel **1401** and the channel **1402**, are monitored.

[**0217**] In one embodiment, monitoring the flow variations in each channel (i.e., **1401**, **1402**) includes plotting the flow variations between each pumping unit (i.e., **1405**, **1427**, **1435**, **1447**) in a channel (i.e., **1401**, **1402**). For example, monitoring the flow variation in each channel (i.e., **1401**, **1402**) includes plotting the flow rate of one pumping unit (i.e., **1405**, **1427**, **1435**, **1447**) relative to another pumping unit (i.e., **1405**, **1427**, **1435**, **1447**) in the channel (i.e., **1401**, **1402**). In another embodiment, monitoring the flow variations may include plotting the metering variations of each pumping unit (i.e., **1405**, **1427**, **1435**, **1447**) in each channel (i.e., **1401**, **1402**). Using FIG. **15**B, graphs of the flow variations within a channel (i.e., **1401**, **1402**) are schematically presented. In one embodiment, the pumping units **1405** and **1427** are positioned in series and pumping units **1435** and **1447** are positioned in series. The graph **1570** represents a piston that is deployed in a pumping unit **1405**, **1435**, positioned in a channel and the graph **1571** represent a piston that is deployed in a pumping unit **1427**, **1447** positioned in the channel. Both graphs (i.e., **1570** and **1571**) display movement of piston versus time as the channel operates. The graph **1572** displays the velocity of a piston (i.e., in a

pumping unit **1405**, **1435** in a channel versus time. The graph **1573** displays the velocity of a piston in a pumping unit **1427**, **1447** in the same channel versus time. A graph of a liquid intake period **1574** into pumping unit **1405**, **1435** is bounded by the vertical axes on each graph and the dashed lines to the right of the vertical axes. A graph of a fast pre-compression jump **1575** of the piston chamber **1406**, **1436** is shown and bounded by vertical dashed lines. **1576** is final compression of the piston chamber **1406**, **1436**. A graph of delivering liquid with the pumping units (i.e., **1405**, **1435**; **1427**, **1447**) within a channel is **1577** is bounded by vertical dashed lines. A graph of the pumping unit **1405**, **1435** delivering the liquid into the pumping system and the pumping unit **1427**, **1447** filled by the pumping unit **1405**, **1435** is shown by **1578**.

[**0218**] Graph **1570** represents the movement of a piston positioned in a pumping unit in a channel. For example, graph **1570** may represent piston **1408** or piston **1438**. Graph **1571** represents the movement of a piston positioned in a pumping unit in a channel. For example, graph **1571** may represent piston **1420** or piston **1448**. During the liquid intake period **1574**, the piston (i.e., **1408** or **1438**) in the channel moves from upper dead center (UDC) to lower dead center (LDC). In addition, the velocity of the pistons (i.e., **1408** and **1420** or **1438** and **1448**) may be shown schematically by graphs **1572** and **1573**. The velocity of the piston (i.e., **1408**, **1438**) within a channel is chosen so that the pumping units **1405** and/or **1435** is outputting liquid within the operating range of the flow sensors **1425** and/or **1430**. Therefore, the flow sensors **1425** and/or **1430** will be able to measure the flow rate. The piston within the channel, such as pistons **1420** and/or **1448**, is then used to deliver the remainder of the requested flow rate (i.e., nominal flow rate). The pressure sensor **1445** positioned at the output **1455** of the pumping system **1400** is used to measure the pressure drop of the pumping system **1400**. In addition, the pressure sensor **1445** is used to correlate the flow rate on the output **1455**.

[**0219**] At step **1562** of FIG. **15**A, the frequently changing relationship between the pumped volume and between two pistons (i.e., **1408** and **1420** and/or **1438** and **1448**) within the same channel is shown as **1577** of FIG. **15**B. The frequently changing relationship of the pump volume between two pumping units within the same channel in combination with different pressure levels corresponding to the frequently changing piston speeds at the output of the pumping system is an indication of a leak. For example, the changing relationship depicted in **1577** of FIG. **15**B displays a dynamic leak in the piston seal **1421** and/or **1449** of FIG. **14** if the pressure sensor **1445** indicates a lower pressure on output **1455** when the volume of liquid output from the piston (i.e., **1420** and/or **1448**) in the channel is higher than the volume of liquid output by the piston **1408** and/or **1438** in the channel **1401** and/or **1402**. It should be appreciated that dynamic leaks in piston/seal combinations can be detected. In a second embodiment, only one channel is connected to pumping system output **1455**.

[**0220**] It should be appreciated that a number of different pumping scenarios may be implemented and still remain in accordance with the teachings of the present invention. It should also be appreciated that individual pumping units may operate at specific times. For example, operating the piston (e.g. **1408** and **1438**) within the channel without operating the piston **1420** and/or **1448** within the channel **1401** and/or **1402** respectively is within the scope of the present invention.

[**0221**] FIG. **15**C displays a flow diagram depicting a method of determining the piston velocity required to produce the nominal (desired) flow rate. In one embodiment, a flow sensor is used to determine a leak rate. A nominal flow rate is determined by performing metering as defined by a metered flow rate, determining the delivered flow rate (i.e., measured flow rate), calculating the leak by comparing metered flow rate and measured flow rate, and calculating correction and/or compensation factors. Metering is then performed to operate the pumping system at the nominal rate. For example, using pumping unit **1405** metering is performed using the motor/encoder system **1414**. The metering outputs liquid from the pumping unit **1405** at a metered flow rate. Flow sensor **1425** is then used to measure the flow rate. The measurement produces a measured flow rate. The difference between the metered flow rate and the measured flow rate is then referred to as the leak rate. The motor/encoder system **1414** then adjusts the operation of the piston **1408** to compensate for the leak rate. In one embodiment, compensating for the leak rate includes adjusting the operation of piston **1408** to produce an additional amount of liquid from pumping unit **1405** to compensate for the liquid lost as a result of the leak.

[**0222**] FIG. **15**C will be discussed in conjunction with FIG. **14**. At step **1580**, a flow sensor is implemented between pumping units within a channel. For example, flow sensor **1425** is positioned between the pumping unit **1405** and pumping unit **1427**. In another embodiment, flow sensor **1430** is positioned between the pumping unit **1435** and pumping unit **1447**. The flow sensors **1425** and/or **1430** may be positioned before the outlet valve **1424** and **1442**, respectively. In a second embodiment, the flow sensors **1425** and/or **1430** may be positioned after the outlet valve **1424** and **1442**, respectively.

[**0223**] At step **1581**, the leakage rate of a piston is determined by metering and measuring the flow as described above. At step **1582**, liquid is taken into the chambers **1406** and/or **1436** in the channels **1401** and **1402**. This requires a downward stroke of the piston **1408** and/or the piston **1438**. In one embodiment of the present invention, the downward stroke is a quick downward stroke. Typically, it is possible to draw in 100 μl liquid within less than 1 second.

[**0224**] At step **1583**, after filling the chamber (**1406** and/or **1436**) in the channel, liquid in the chambers **1406** and/or **1436** is compressed. In one embodiment, the liquid is compressed rapidly. For example, in one embodiment compress chamber **1406** and/or chamber **1436** rapidly. In one embodiment, the initial upward stroke of the piston **1408** and the piston **1438** is performed quickly within 100 ms.

[**0225**] At step **1584**, when the liquid in the chamber is fully compressed, open the outlet valve. For example, after the liquid stored in chambers **1406** and/or **1436** is fully compressed, open the outlet valves **1424** and/or **1442**. At step **1585**, a flow sensor, such as flow sensors **1425** and/or **1430** are used to detect the measured rate. Once the outlet valves (i.e., **1424** and/or **1442**) are opened, the flow sensors (i.e., **1425** and/or **1430**) will detect the flow rate delivered by pistons **1408** and **1438**. Since the flow sensors **1425** and/or **1430** are calibrated, the reading attained from the flow

sensors **1425** and/or **1430** is the actual (i.e., measured) flow rate and can be determined by reading the flow sensor as stated at **1585**. At step **1586**, the encoder located in the motor/encoder system is read. The number of steps produced by the motor/encoder system is equal the metered flow rate. At step **1587**, compare the actual flow rate with the metered flow rate. At step **1588**, a comparison of the actual (i.e., measured) flow rate and the metered flow rate is performed to calculate the leak. Once the leak has been calculated, the leak can be compensated for by metering at a new calculated piston velocity, etc.

[**0226**] A second method of determining the piston velocity required to produce the nominal (desired) flow rate is presented. In the second method, a leak is determined in an outlet valve when a second piston is pumping. In one embodiment, the method depicted in the flow diagram of **13**B is implemented.

[**0227**] In the second method of determining the piston velocity required to produce the nominal flow rate when a leak is determined in the outlet valve and the second piston in the channel is pumping. For example, at step **1347** of FIG. **13**B, the chamber **1428** and/or **1446** in the channel **1401** and/or **1402** is filled. The outlet valve **1424** and/or **1442** is closed and the piston **1421** and/or **1449** in the channel performs a delivery stroke. A flow sensor **1425** and/or **1430** positioned between the pumping unit **1405** and/or **1435** and the pumping unit **1427** and/or **1447** in the channel **1401** and/or **1402** is then used to measure backflow as stated step **1349** of FIG. **13**B. The backflow is equivalent to the amount of the leak; therefore, the backflow is used to determine the leak as stated at **1350** of FIG. **13**B. The piston **1421** and/or **1449** is then adjusted to compensate for the leak as stated at **1351** of FIG. **13**B. In one embodiment, compensating for the leak includes calculating a new piston velocity required to produce the nominal or desired flow rate at the output. Using FIG. **14** to discuss the method, chambers **1427** and/or **1447** are filled with liquid. Outlet valves **1424** and/or **1442** are closed. Pistons **1421** and/or **1448** perform a delivery stroke. Flow sensors **1425** and/or **1430** are used to measure any flow of liquid. A flow of liquid indicates a leak in outlet valve **1424** and/or outlet valve **1442**. The leak is equivalent to the flow of liquid. A new piston velocity may then be determined to compensate for the leak. The new piston velocity may be calculated by computer **1417** and implemented by motor/encoder system **1415** and/or **1450**, respectively. Once the compensation is made, a nominal flow rate will be produced at the output **1455**.

[**0228**] It should be appreciated that once the outlet valve **1424** and/or **1442** is opened and the piston chamber **1428** and/or **1446** is fully compressed, the creeping effect of the pumping system **1400** must be considered when calculating the leak rate. Creeping is a natural function of the pumping system **1400** in which the components of the pumping system **1400** settle. During creeping, some leakage may occur; however, once creeping effects have terminated, the pumping system **1400** should operate in steady state (i.e., with or without leakage).

[**0229**] In one embodiment, a method of determining leaks when the flow rate is higher than the range of the flow sensor is presented. A chamber in a first pumping unit is filled with fluid. At the same time that the chamber in the first pumping unit is being filled with fluid, the second pumping unit is delivering the desired flow rate. After filling the first pumping unit, the piston in the first pumping unit moves upward to compress the liquid in the first chamber at the same time the second piston is delivering the desired flow rate. Once the compression is complete, the outlet valve associated with the first pumping unit is opened. Afterwards, the first pumping unit delivers a portion of total flow rate into the system. The portion of the total flow rate is selected within the range of the flow sensor. A leak is then determined. The difference between the metered flow rate and the measured flow rate defines the leak. At the same time, the second piston delivers the remainder (nominal flow rate−measured flow rate) of the desired flow rate into the system. In the case where the first piston is delivering the total flow rate into the system, the metered flow rate is equivalent to the nominal flow rate plus the leak (i.e., nominal flow rate+the leak).

[**0230**] Using FIG. **14**, chambers **1406** and/or **1436** in pumping units **1405** and/or **1435** are filled with liquid. At the same time that chambers **1406** and/or **1436** are being filled with liquid, pumping units **1427** and/or **1449** are delivering the desired flow rate. After filling chambers **1406** and/or **1436**, pistons **1408** and/or **1438**, respectively, move upward to compress the solvent in chambers **1406** and/or **1436** at the same time that pistons **1420** and/or **1448** are delivering the desired flow rate. Once the compression is complete, the outlet valves **1424** and/or **1442** associated with the pumping units **1405** and/or **1435** are opened. Afterwards, the pumping units **1405** and/or **1435** deliver a portion of total flow rate into the system. The portion of the total flow rate is selected within the range of the flow sensors **1425** and/or **1430**. A leak is then determined. The difference of metered flow rate and measured flow rate defines the leak. At the same time, the second pistons **1420** and/or **1448** delivers the remainder (nominal flow rate−measured flow rate) of the desired flow rate into the system. In the case where the pistons **1408** and/or **1438** are delivering the total flow rate into the system, the metered flow rate is equivalent to the nominal flow rate plus the leak (i.e., nominal flow rate+the leak).

[**0231**] FIG. **15**D includes a flow diagram depicting a method of monitoring compression phases in a pumping chamber and monitoring the system pressure of a chromatographic system. In one embodiment, a single pressure sensor, such as pressure sensors **1407** and/or **1431** are required to monitor compression phase of chambers **1406** and/or **1436** and to monitor system pressure of the chromatographic system. FIG. **15**D will be described in conjunction with FIG. **14**.

[**0232**] At step **1590**, solvent (i.e., liquid) is delivered into a pumping system using a second pumping unit. At step **1591**, the first piston is used to rapidly intake liquid into the chamber in the first pumping unit (i.e., first pumping chamber). At step **1592**, pressure is measured within the chamber of the first pumping unit. At step **1593**, the liquid in the first pumping chamber is immediately compressed. At step **1594**, the pressure in the first pumping chamber is measured during the compression phase with the pressure sensor in the first pumping chamber. At step **1595**, the outlet valve associated with the first pumping chamber is immediately opened. At step **1596**, the pressure in the first pumping chamber may be used to measure the system pressure of the pumping system **1400**. At step **1597**, the outlet valve is kept opened by pumping a small amount of liquid until the second chamber must be refilled. At step **1598**, monitor the

system pressure and blockages with the pressure sensor in the first pumping chamber. At step **1599**, delivery of liquid into the system is stopped if a system blockage is detected.

[**0233**] FIG. **14** will be used to demonstrate the method detailed in the flow diagram in FIG. **15**D. At step **1590**, solvent (i.e., liquid) is delivered into the system using a second pumping unit. Therefore, pumping unit **1427** and/or pumping unit **1447** are used to deliver liquid into the system. At step **1591**, the pistons **1408** and/or **1438** rapidly intake solvent into the chambers **1406** and/or **1436** in the pumping units **1405** and/or **1435**. Pumping units **1405** and/or **1435** rapidly intake liquid into chambers **1406** and **1436**, respectively. At step **1592**, pressure is measured within the chamber **1406** and/or **1436** of the pumping units **1405** and/or **1435**. Pressure sensor **1407** is used to measure the pressure of chamber **1406** and/or pressure sensor **1431** is used to measure the pressure of chamber **1436**. At step **1593**, the liquid in the chamber **1406** and/or **1436** is immediately compressed. Piston **1408** is used to compress liquid such as solvent stored in chamber **1406** and/or piston **1438** is used to compress liquid such as solvent stored in chamber **1436**. At step **1594**, the pressure in the chamber **1406** and/or **1436** is measured during the compression phase with the pressure sensor **1406** and/or **1431** in the chamber **1406** and/or **1436**. As piston **1408** is compressing the liquid in chamber **1406**, pressure sensor **1407** is used to measure the pressure in chamber **1406**. As piston **1438** compresses liquid in chamber **1436**, pressure sensor **1431** is used to measure the pressure in chamber **1436**. At step **1595**, the outlet valve associated with the first pumping chamber is immediately opened. Outlet valve **1424** and/or outlet valve **1442** is immediately opened. At step **1596**, the pressure in the first pumping chamber may be used to measure the system pressure of the pumping system **1400**. After opening outlet valves **1424** and/or **1442**, pressure sensor **1407** and/or pressure sensor **1431** may be used to measure the system pressure. At step **1597**, the outlet valve is kept opened by pumping a small amount of liquid until the second piston must be refilled. Outlet valve **1424** and/or outlet valve **1442** remains open and piston **1408** and/or piston **1438** deliver a small amount of liquid until the second pumping unit **1427** and/or **1447** must be refilled. At step **1598**, monitor the system pressure and blockages with the pressure sensor in the first pumping chamber. Pressure sensor **1407** and/or pressure sensor **1431** are used to measure system pressure to detect blockage in the pumping system **1400**. Changes in pressure measured by pressure sensor **1407** and/or pressure sensor **1431** when the pressure sensors (i.e., **1407** and/or **1431**) are used to measure system pressure will signal a blockage in the pumping system. At step **1599**, delivery of liquid into the system is stopped if a system blockage is detected. If a blockage is detected, delivery of solvent with pumping units **1427** and/or **1447** is terminated.

[**0234**] FIG. **16**. displays a pumping system **1600**. The pumping system **1600** includes a channel **1610** and a channel **1620**. The channel **1610** includes a pumping unit **1612** in series with a pumping unit **1614**. The channel **1620** includes a pumping unit **1622** in series with a pumping unit **1624**. A reservoir **1602** stores a first liquid. A reservoir **1604** stores a second liquid. A channel output **1630** is connected to channel **1610**. A channel output **1642** is connected to channel **1620**. A pressure sensor **1632** is positioned on the channel output **1630**. Channel output **1630** is connected to a waste output **1633** through a T-junction **1637**. A purge valve **1634** is positioned on the waste output **1633**. A waste exhaust **1636** provides an output for liquid conveyed on the waste output **1633**.

[**0235**] A T-junction **1640** provides a connection between the channel output **1642** and a system output **1641**. The system output **1641** provides a pathway to the chromatography system as shown by **1645**. A conveyance **1639** is shown between T-junction **1637** and T-junction **1640**. In one embodiment, a flow sensor **1638** is positioned along the conveyance **1639**. In another embodiment, the flow sensor **1638** is not included in the pumping system. It should also be appreciated that in an alternate embodiment, the T-junction **1637**, the purge valve **1634**, the waste output **1633**, and the waste exhaust **1636** may be positioned in channel output **1642**.

[**0236**] During operation, a liquid is pumped through the channel **1610** to the channel output **1630** and through the channel **1620** to the channel output **1642**. A mixture of the channel output **1630** and the channel output **1642** is combined at a mixing point identified by the T-junction **1640** and conveyed on a pumping system output **1641** to the system as shown at **1645**. It should be appreciated that while an embodiment of a specific pumping unit is detailed in each channel (i.e., **1610**, **1620**), the present invention may be directed to pumping systems with different channel components (i.e., pumping units, valves, etc.). It should also be appreciated that more than two channels may be connected at T-junction **1640**. In addition, waste from channel output **1630** and channel output **1642** may travel along waste output **1633**, through the purge valve **1634** and through the waste exhaust **1636**.

[**0237**] FIG. **16**A displays a flowchart depicting a method of flushing a pumping system completely. FIG. **16**A will be discussed in conjunction with FIG. **16**. At step **1650** of FIG. **16**A, a purge valve, such as purge valve **1634**, is opened. At step **1652**, the channel that the purge valve **1634** is positioned in is flushed. For example, using FIG. **16**, the first channel **1610** is flushed. Flushing the first channel **1610** includes conveying liquid on channel output **1630**, through T-junction **1637**, through waste output **1633**, through purge valve **1634**, and through waste exhaust **1636**. At step **1654**, the channel that the purge valve **1634** is not positioned in is flushed. For example, the second channel **1620** is flushed. Flushing the second channel **1620** includes conveying liquid on channel output **1642**, through T-junction **1640**, through conveyance **1639**, through T-junction **1637**, through waste output **1633**, through purge valve **1634**, and through waste exhaust **1636**. As an optional step, at step **1656**, both channels **1610** and **1620** may be flushed together. At step **1658**, the channel that the purge valve **1634** is positioned in is flushed one more time. For example, channel **1610** is flushed again. At step **1660**, the purge valve, such as purge valve **1634**, is closed. At step **1662**, a decision is made on how to flush the conveyance **1639** between the two T-junctions (i.e., **1637** and **1640**) with liquid from the channel the purge valve **1634** is positioned. For example, this would include flushing conveyance **1639** with liquid flowing through channel output **1630**. If the decision is made to flush the conveyance **1639** via the system output **1641**, then solvent is pumped from the channel that the purge valve **1639** is positioned in until liquid is at the mixing point. This has the effect of cleaning the conveyance between the two T-junctions of liquid from the second channel. Using FIG.

16 as an example, this would include pumping liquid from channel 1610, through the channel output 1630, across T-junction 1637, across conveyance 1639 to a mixing point defined by the location where channel output 1630, channel output 1642, and pumping system output 1641 meet in T-junction 1640. After step 1664, normal operation is continued as shown at 1666.

[0238] If a decision is made not to flush the conveyance between the two T-junctions (i.e., 1637 and 1640) via the pump system outlet 1641 as stated at 1662, then as stated at step 1668, solvent is pumped from the channel that the purge valve is positioned in backwards to the channel that the purge valve is not positioned in until the correct solvents occur at a defined mixing point. Using FIG. 16, this would mean pumping liquid from channel 1610 along channel output 1630, past T-junction 1637, along conveyance 1639, past T-junction 1640 backwards into channel output 1642. After step 1668, normal operation is continued as shown at 1669.

[0239] FIG. 16B displays a flowchart depicting a method of compensating for a leak in multi-channel pumping system. FIG. 16B will be discussed in conjunction with FIG. 16. At step 1670, a pumping system, such as pumping system 1600, is operating. At step 1672, the pumping in one channel is stopped. At step 1674, the backflow into the stopped channel is detected. At step 1676, the backflow into the stopped channel is used to calculate the amount of the leak. At step 1678, the leak is compensated for. The leak may be compensated for in a number of different ways. In one embodiment, at step 1680, a small amount of flow is delivered to maintain zero flow at the channel output. In another embodiment, at step 1682 the leak is stored in the stopped channel output. The channel output itself is cleaned from time to time by delivering the stored leak.

[0240] The method depicted by the flowchart of FIG. 16B will be discussed in conjunction with the pumping system 1600 of FIG. 16. At step 1670, the pumping system 1600 is operating. At step 1672 one channel, such as channel 1610, is stopped. At step 1674, the backflow into channel 1610 is sensed. In one embodiment, the backflow into channel 1610 is sensed in the flow sensor 1638. At step 1676, the amount of leak in the channel 1610 is calculated. The leak may be calculated using a number of the foregoing techniques presented in the instant application. For example, in one embodiment, the leak equals the measured flow minus the metered flow determined by the pumping units 1612 and 1614. At step 1680, a small amount of flow is delivered to maintain a zero flow at the mixing point. For example, an amount of flow equal to the leak may be generated dynamically to maintain a zero flow at the mixing point defined by T-junction 1640. Delivering the flow equal to the leak will include operating channel 1610 to generate an amount equivalent to the leak and a zero flow at T-junction 1640. In an alternate embodiment, at step 1682, an amount of liquid equivalent to the amount of leak is stored in the channel output 1630. The channel is cleaned from time to time preferable when the chromatography is not influenced.

[0241] Thus, the present invention has been described herein with reference to a particular embodiment for a particular application. Those having ordinary skill in the art and access to the present teachings will recognize additional modifications, applications, and embodiments within the scope thereof.

[0242] It is, therefore, intended by the appended claims to cover any and all such applications, modifications, and embodiments within the scope of the present invention.

What is claimed is:

1. A pumping system comprising:

a first channel pumping first fluid;

a first channel output coupled to the first channel and outputting first fluid in response to the first channel pumping first fluid;

a conveyance having an inlet and an outlet, the inlet coupled to the first channel output;

a second channel pumping second fluid;

a second channel output coupled to the second channel and outputting second fluid in response to second channel pumping second fluid;

a waste output having a valve coupled to the first channel output and coupled to the conveyance inlet, the waste output conveying waste in response to opening the valve; and

a system output coupled to the outlet of the conveyance and coupled to the second channel output, the system output conveying output fluid in response to closing the valve.

2. A pumping system as set forth in claim 1, further comprising a flow sensor coupled to the conveyance, the flow sensor detecting fluid flow.

3. A pumping system as set forth in claim 1, further comprising a flow sensor coupled to the second channel output and measuring fluid flow in response to the second fluid output on the second channel output.

4. A pumping system as set forth in claim 1, further comprising a filter coupled to the channel output.

5. A method of operating a pumping system, the pumping system comprising a first channel transporting first fluid, a second channel transporting second fluid, a waste output having a valve coupled to the first channel and coupled to the second channel via a conveyance, the waste output adapted for transporting waste, a system output coupled to the first channel via the conveyance and coupled to the second channel, the system output adapted for transporting system fluid, the method comprising:

opening the valve;

flushing the second channel in response to opening the valve;

flushing the first channel in response to flushing the second channel;

closing the valve in response to flushing the first channel; and

pumping solvent from the first channel through the conveyance.

6. A method of operating a pumping system as set forth in claim 5, wherein pumping solvent from the first channel through the conveyance further comprises back-flushing the solvent into the second channel.

7. A method of operating a pumping system, the pumping system comprising a first channel transporting first fluid, a second channel transporting second fluid, a waste output having a valve coupled to the first channel and coupled to the

second channel via a conveyance, the waste output adapted for transporting waste, a system output coupled to the first channel via the conveyance and coupled to the second channel, the system output adapted for transporting system fluid, the method comprising:

opening the valve;

flushing the first and second channel in response to opening the valve;

flushing the first channel in response to flushing the first and second channel;

closing the valve in response to flushing the first channel; and

pumping solvent from the first channel through the conveyance.

8. A method of operating a pumping system as set forth in claim 7, wherein pumping solvent from the first channel through the conveyance further comprises back-flushing the solvent into the second channel.

9. A software program or product, preferably stored on a data carrier, for controlling or executing A method of operating a pumping system, the pumping system comprising a first channel transporting first fluid, a second channel transporting second fluid, a waste output having a valve coupled to the first channel and coupled to the second channel via a conveyance, the waste output adapted for transporting waste, a system output coupled to the first channel via the conveyance and coupled to the second channel, the system output adapted for transporting system fluid, the method comprising: opening the valve; flushing the second channel in response to opening the valve; flushing the first channel in response to flushing the second channel; closing the valve in response to flushing the first channel; and pumping solvent from the first channel through the conveyance, when run on a data processing system such as a computer.

10. A system adapted to execute or control a method of operating a pumping system, the pumping system comprising a first channel transporting first fluid, a second channel transporting second fluid, a waste output having a valve coupled to the first channel and coupled to the second channel via a conveyance, the waste output adapted for transporting waste, a system output coupled to the first channel via the conveyance and coupled to the second channel, the system output adapted for transporting system fluid, the method comprising: opening the valve; flushing the second channel in response to opening the valve; flushing the first channel in response to flushing the second channel; closing the valve in response to flushing the first channel; and pumping solvent from the first channel through the conveyance.

11. The system of claim 10 comprising:

a channel conveying a fluid at a flow rate; and

a flow sensor positioned within the channel, the flow sensor capable of detecting the flow rate.

12. The system as set forth in claim 11,

the channel comprising a first pumping unit and a second pumping unit, wherein the first pumping unit and the second pumping unit are positioned in series or in parallel;

further comprising at least one of:

the flow sensor is positioned between the first pumping unit and the second pumping unit;

the flow sensor is positioned before the first pumping unit;

the flow sensor is positioned after the second pumping unit;

the flow sensor is positioned before the first pumping unit and a second flow sensor is positioned before or after the second pumping unit;

the flow sensor is positioned after the first pumping unit and a second flow sensor is positioned after the second pumping unit.

13. The system as set forth in claim 11, comprising at least one of:

a second channel coupled to the first channel, the second channel conveying a second fluid at a second flow rate; wherein preferably a second flow sensor positioned within the second channel and capable of detecting the second flow rate.

14. The system as set forth in claim 11, the channel comprising:

a first pumping unit;

a drive system coupled to the first pumping unit and causing the first pumping unit to pump a fluid at a flow rate;

a second pumping unit coupled to the first pumping unit and receiving at least a portion of the fluid;

a second drive system coupled to the second pumping unit and causing the second pumping unit to pump the fluid.

15. The pumping system as set forth in claim 11, the channel comprising:

a first pumping unit;

a first drive system coupled to the first pumping unit and causing the first pumping unit to pump a first fluid at a first flow rate;

a second pumping unit;

a second drive system coupled to the second pumping unit and causing the second pumping unit to pump a second fluid at a second flow rate.

16. The system according to claim 11, wherein the first flow rate is substantially similar to the second flow rate.

17. The system as set forth in claim 11, further comprising at least one of:

a computer coupled to at least one of the first and the second drive system;

the computer being adapted for controlling each coupled to drive system, preferably controlling the movement of each coupled to drive system.

18. The system as set forth in claim 11, comprising at least one of:

wherein the pumping system is a low-pressure gradient pumping system;

the pumping system is a high-pressure gradient pumping system;

the pumping system further comprising a first driving unit coupled to and operating the first pumping unit and a second driving unit coupled to and operating the second pumping unit;

the pumping system operates at a high system pressure;

the flow sensor is capable of measuring flow independent of flow direction;

the flow sensor is calibrated for the solvent pumped in the first channel;

at least one of a switching valve and a proportioning valve coupled to the conveyance and capable of switching fluid onto the conveyance.

19. An analysis system comprising a system according to claim 9, comprising at least one of:

the analysis system is a chromatography system, preferably a High Pressure Liquid Chromatography system;

a column adapted for separating compounds of the fluid;

a sensor adapted for sensing separated compounds of the fluid;

a sampler adapted for introducing samples to be separated into the fluid;

a fractionator adapted for outputting separated compounds of the fluid.

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